# RECORD OF UPDATES

<table>
<thead>
<tr>
<th>NO</th>
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<tbody>
<tr>
<td>1</td>
<td>March, 1997</td>
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<tr>
<td>2</td>
<td>September, 2000</td>
</tr>
<tr>
<td>3</td>
<td>September, 2016</td>
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HOW TO USE THE GUIDELINES

The Ontario Guidelines for Drug Submission and Evaluation (the Guidelines) were developed to provide manufacturers with practical information and guidance to facilitate the submission of information to the Ministry of Health and Long-Term Care (“ministry”) and to provide a better understanding of the submission evaluation and approval process. This document should be read in conjunction with the governing statutes and regulations. In the event of a conflict or discrepancy between these Guidelines and the regulations under the Ontario Drug Benefit Act (“ODBA”) or the Drug Interchangeability and Dispensing Fee Act (“DIDFA”), the regulations prevail.

Note: Any updates to the Guidelines will be published on the ministry’s website, and are effective as of that date unless otherwise specified. It is the manufacturer’s responsibility to meet all current regulatory and submission requirements for all submissions to the Ontario Public Drug Programs.

INQUIRIES AND ASSISTANCE

Inquiries and correspondence related to this publication should be directed to:

Director
Drug Programs Policy and Strategy Branch
Ontario Public Drug Programs
Ministry of Health and Long-Term Care
3rd Floor, 5700 Yonge Street
Toronto ON M2M 4K5
Telephone: (416) 327-8109
Fax: (416) 327-8123
Email: DrugBenefits@ontario.ca
Please note: manufacturer submissions must be sent to the address noted below. Do not send submissions to 80 Grosvenor, 9th Floor Hepburn address. This may result in delays in processing submissions.

All submissions and any additional related information must be sent to:

Senior Manager
Drug Benefits Management
Drug Programs Policy and Strategy Branch
Ontario Public Drug Programs
Ministry of Health and Long-Term Care
3rd Floor, 5700 Yonge Street
Toronto, ON M2M 4K5

All requests with respect to pricing negotiations must be sent directly to:

Director
Drug Programs Policy and Strategy Branch
Ontario Public Drug Programs
Ministry of Health and Long-Term Care
80 Grosvenor Street
9th Floor, Hepburn Block Toronto, ON M7A 1R3

Please note that the Ontario Public Drug Programs operates from two different locations, as noted above. The ministry is not responsible for misdirected correspondence sent to the wrong location or for any delays in the processing of a submission resulting therefrom.
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LIST OF ABBREVIATIONS
LIST OF ABBREVIATIONS

**Acronyms:**

- ANDS: Abbreviated New Drug Submission
- BIA: Budget Impact Analysis
- CADTH: Canadian Agency for Drugs and Technologies in Health
- CAP: Clinical Assessment Package
- CCO: Cancer Care Ontario
- CDEC: Canadian Drug Expert Committee
- CDR: Common Drug Review
- CED: Committee to Evaluate Drugs
- CPID: Certified Product Information Document
- CRP: Canadian Reference Product
- DBP: Drug Benefit Price
- DIDFA: Drug Interchangeability and Dispensing Fee Act
- DIDFA Regulation: Regulation 935 made under the DIDFA
- DIN: Drug Identification Number
- DNF: Drug Notification Form
- DoE: Declaration of Equivalence
- DQTC: Drug Quality and Therapeutics Committee
- DSG: Drug Submission Group
- EAP: Exceptional Access Program
- EO: Executive Officer
- HC: Health Canada
- MAR: Maximum Allowable Reimbursement
- N/A: Not Applicable
- NAB: Not-A-Benefit
- NCRP: Non-Canadian Reference Product
<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<td>NDFP</td>
<td>New Drug Funding Program</td>
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<td>NDS</td>
<td>New Drug Submission</td>
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<td>NDSS</td>
<td>Notice of Drug Submission Status</td>
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<td>NHP</td>
<td>Natural Health Product</td>
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<td>NOC</td>
<td>Notice of Compliance</td>
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<td>NOC/S</td>
<td>Supplemental NOC</td>
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<td>NOC/c</td>
<td>Conditional Notice of Compliance</td>
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<td>NOL</td>
<td>No Objection Letter</td>
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<td>ODB</td>
<td>Ontario Drug Benefit</td>
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<td>ODBA Regulation</td>
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<td>Off-Formulary Interchangeability</td>
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<td>pan-Canadian Oncology Drug Review</td>
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<td>pERC</td>
<td>pCODR Expert Review Committee</td>
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<td>PM</td>
<td>Product Monograph</td>
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<td>PMPRB</td>
<td>Patented Medicine Prices Review Board</td>
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<tr>
<td>OTC</td>
<td>Over-the-Counter</td>
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<tr>
<td>QALY</td>
<td>Quality-Adjusted Life Year</td>
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<td>SDP</td>
<td>Special Drugs Program</td>
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<td>TDSPA</td>
<td>Transparent Drug System for Patients Act, 2006</td>
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EXECUTIVE SUMMARY
EXECUTIVE SUMMARY

INTRODUCTION

The Ontario Public Drug Programs (OPDP) provides funding for a number of public 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 Ontario Public Drug Program, a drug manufacturer must provide a complete submission in accordance with the prescribed conditions set out in Ontario Regulation 201/96 made under the Ontario Drug Benefit Act (the “ODBA Regulation”) and Regulation 935 made under the Drug Interchangeability and Dispensing Fee Act (the “DIDFA Regulation”), and these Guidelines.

The regulations are available on the e-Laws at http://www.e-laws.gov.on.ca

OVERVIEW OF CHANGES IN SUBMISSION REQUIREMENTS, POLICY AND REVIEW PROCESS

Below are some of the key changes to the regulations after the publication of the Ontario Drug Submission and Evaluation Guidelines 2000 that affect the submission requirements. In addition, the ministry also updated policy requirements to be consistent with the new changes.

Please note that this section is only intended to highlight the key changes made since 2000 and is not an exhaustive list. In addition, all of these changes have already been incorporated in the current submissions screening and review process since 2000.
Changes to Regulations

- Exempting dermatological products that contain one or more glucocorticoids as the only active ingredient and transdermal drug products for systemic effect from the regulatory requirement for conducting an in-vivo bioequivalence study when Health Canada has granted a declaration of equivalence (DoE) with the original product. (Refer to Part III-B.2.l & m)

- Allowing certain aqueous solutions to be exempt from completing an in-vivo bioequivalence study regardless of package size if pharmaceutical equivalence is demonstrated. (Refer to Part III-B.2.e)

- With limited exceptions, interchangeable drug products must be priced at a maximum of 25 percent of the listed original product (the “25% pricing rule” or Tiered Generic Pricing Framework). (Refer to Part III-A-4 or Part III-B.1.h)

- The Executive Officer may consider making an interchangeability designation in respect of products containing a drug or drugs in the same amounts of the same or similar active ingredients in the same or similar dosage form. (Refer to Part III-B.2.j)

- The manufacturer must certify in writing that no rebates were provided to persons listed under subsection 12.1(1) of the DIDFA with respect to the drug product from the time that Health Canada approved the product for sale in Canada. (Refer to Part III-A.1.i or to Part III-B.1.j)

- A rapid review mechanism for (brand) single source product allows manufacturers to make a submission for a drug product prior to it receiving Health Canada’s Notice of Compliance (pre-NOC submission) if specific criteria are met. (Refer to Part III-A.1.c.)

- The manufacturer (brand and generic) must submit a letter confirming that the submitted drug product is not a private label product (Refer to PART III-A.1.m or PART III-B.1.m). To assist manufacturers, the ministry has developed a template letter which is available on the ministry’s website.

Changes in Submission Policy

- Submission requirement for the number of hard copies and electronic copies (CDs, DVDs or USB keys) for Multiple Source Submissions, Diabetic Strips, Nutrition Products and for Single Source Submissions. The electronic copies
must be provided in MS Word or PDF format that is unlocked, searchable and printable allowing the users to extract information or combine documents. The ministry will accept CDs, DVDs or USB keys electronic copy. (Refer to PART II-A.1.)

- The ministry will only accept a Non-Canadian Reference Product (NCRP) as equivalent to the Canadian Reference Product if that NCRP conforms to the criteria established by, and has been approved by, Health Canada. (Refer to Part III-B.2.i)

- In order to mitigate the risk of regulatory breach or inducing patent infringement, the ministry requires manufacturers to advise the ministry that there are no outstanding patent issues for the proposed drug product submission. Manufacturers must provide confirmation of patent status for the multiple source drug products (ODB benefit and OFI products). (Refer to Part III-B.1.k.)

- It is a condition for an approved drug product to be readily available at the time of listing on the Formulary and be able to meet the anticipated demand at the time of listing on the Formulary. In the event the ministry is notified of the inability to supply the drug product at the time of listing or shortly thereafter the listing, the drug product may be removed (delisted) from the Formulary listing. (Refer to Part III-A.1.h. or Part III-B.1.i.)

- The ministry will only accept another listed interchangeable product as the reference product, if the original product is no longer marketed. (Refer to Part III-B.2.k)

- The ministry has harmonized and streamlined its scientific review of multiple-source products with Health Canada for certain multiple source products where Health Canada has declared equivalence on the product’s Notice of Compliance, the ministry will not consider challenges for these “streamlined” submissions. Challenges to this designation should be referred to Health Canada. (Refer to Part II-A.9)

- The ministry will accept a challenge that is relevant to the consideration of a non-streamlined submission. In general, the CED will consider only one challenge for a given product based on first challenge received by the ministry. (Refer to Part II-A.9)
• Manufacturers have a nine-month (180 business days) period to respond to the negative recommendation from the Committee for Drug evaluation (CED). If a manufacturer fails to address the outstanding issues within that time period, the submission may be withdrawn and subsequently destroyed. Please note that after two reconsiderations, the manufacturer must provide a new submission with substantive new clinical or economic data for further consideration by the CED. (Refer to Part II-A.4)

• The ministry will only review submissions for new OTC drug products on a case-by-case basis. These products are subject to the regulatory requirements under the ODBA and the DIDFA and the requirements set out in the Guidelines. OTC product regulated under the Natural Health Products Regulations will not be considered. (Refer to Part II-B.5)

• The ministry reimburses a limited number of Natural Health Products (NHPs) that are listed as benefits on the Formulary at the time of submission. The ministry, however, will not consider adding new NHPs to the Formulary. Submission requirements for interchangeable NHP and transitional NHP are available. (Refer to Part II-B.6)

• The ministry will not accept or consider submissions for any OTC products, NHP or NDFP products for OFI interchangeability. (Refer to Part VI)

• The ministry will no longer issue a confirmation letter for the complete submission for multiple source submissions for the notice of change in the PM to match the innovator PM. The manufacturers will only be asked to respond to the Branch if additional information is required to complete the submission. That is only incomplete letters will be issued to the manufacturers. (Refer to Part III-B.5.b.1)

• All drug products reviewed by the Common Drug Review (CDR) and the pan-Canadian Oncology Drug Review (pCODR) will no longer require a routine review by the Committee to Evaluate Drugs (CED), the ministry’s expert drug advisory committee. On a case-by-case basis, the Ontario Public Drug Programs (OPDP) may seek CED’s advice on drug products previously reviewed by the CDR or pCODR. (Refer to Part II-A.3)

• In order for a multiple source drug product (ODB benefit and OFI) to be considered for inclusion in the next monthly Formulary update by the Executive Officer, the submission must be received by the new submission deadline (date and time). There are no exceptions for late submissions. If a submission is incomplete, the manufacturer must wait until the following monthly new
submission deadline before its drug product submission will be screened after receipt of additional information. All submissions will be held to a strict compliance standard as evaluated against the submission requirements and procedures set out under the *Ontario Drug Benefit Act*, the *Drug Interchangeability and Dispensing Fee Act* and the ministry’s policy. (Refer to Part II-A.1.)

- It is the ministry’s policy that when any of the submission documents or materials is found to be deficient in any respect, irrespective of whether the deficiency goes to form or content, the submission request for the proposed listing of the drug product on the Formulary will be deemed incomplete. There are no exceptions for any type of deficiency. The policy will apply to all product submissions and drug product submissions for single source and multiple source products (streamlined and non-streamlined), irrespective of whether they are being proposed for an interchangeability and/or a benefit designation on the Formulary or for inclusion on the Off-Formulary Interchangeability (OFI) list. The onus is on the manufacturer to provide the ministry with complete and accurate information regarding its submission to avoid delays in the listing of their products. (Refer to Part II-A.1)

- The ministry has adopted Health Canada’s testing parameters (universal tests and specific tests and container closure system tests) to replace the current testing requirements for the aqueous solutions under subsection 6(5). (Refer to Part III-B.2.e.)

- The original and/or most recent Notice of Compliance (NOC) and a most recent Drug Product Monograph with the date of revision must be provided. (Refer to PART III-A.1.c or PART III-B.1.c)

- The manufacturer must confirm the Drug Notification Number (DIN) for the products if it does not appear on the supplemental Notice of Compliance. That is the original NOC must also be provided. (Refer to PART III-A.1.c or PART III-B.1.c)

- When there is change in the Product Monograph, the manufacturer must submit the most recent Product Monograph with control number, the date of revision, and tracked changes (as well as evidence that Health Canada has approved the changes [i.e., Letters of No Objection, Supplemental NOC, etc.]). (Refer to PART III-A.1.c or PART III-B.1.c)
INTRODUCTION
**OBJECTIVE**

The Guidelines are to be used in the preparation of a drug product submission provided to the ministry. Some sections of the Guidelines are general in nature and must be read in conjunction with the complete provincial drug legislative and regulatory framework. The manufacturers or those filing submissions on their behalf should ensure that all drug product submissions filed with the ministry contain sufficient information to satisfy the requirements of the *Ontario Drug Benefit Act* and its regulation, the *Drug Interchangeability and Dispensing Fee Act* and its regulation, and the Guidelines.

The purpose of the Guidelines is to assist the drug manufacturers with the preparation of a well-structured drug product submission to facilitate the screening and subsequent review by the ministry. It should be noted that all requirements in the Guidelines may not necessarily apply to every product. Data requirements will vary depending on the submission type.
SCOPE

The Guidelines cover the preparation and filing of the following drug product submissions, filed pursuant to Ontario Regulation 201/96 made under the Ontario Drug Benefit Act (the “ODBA Regulation”) and Regulation 935 made under the Drug Interchangeability and Dispensing Fee Act (the “DIDFA Regulation”):

- New Chemical Entities and New Combination Products;
- Single Source Products that do not contain New Chemical Entities;
- Requirements in Specific Cases (e.g., Brand Line Extension Products, Drug Products without official product monograph, Pseudogeneric Products);
- Interchangeable Product Submissions;
- Over-the-Counter Drug Products;
- Oncology Drug Products;
- Special Drugs Program Products; and
- Off-Formulary Interchangeability (OFI) Drug Products.

The Guidelines also includes the preparation and filing of the following product submissions:

- Natural Health Products;
- Diabetic Testing Agents; and
- Nutrition Products.

The ministry strongly recommends that manufacturers follow the Guidelines when preparing submissions for the ministry. The onus is on the manufacturer to provide the ministry with a submission that is complete and accurate and compliant with 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. Notwithstanding the foregoing, the ministry reserves the right to request additional information at any time.

PART I

ABBREVIATED LISTS OF DRUG PRODUCT SUBMISSION REQUIREMENTS
PART I ABBREVIATED LISTS OF DRUG PRODUCT SUBMISSION REQUIREMENTS

The submission should include the following requirements as applicable.

**NOTE:** This section is only a summary and is intended to provide an overview of the submission requirements. Please refer to Part II and III of the Guidelines for a review of the comprehensive requirements.

<table>
<thead>
<tr>
<th>(ODBA) SINGLE SOURCE (ORIGINAL) PRODUCTS, LINE EXTENSIONS, NEW INDICATIONS (i.e., BENEFIT)</th>
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<tr>
<td>1. Cover Letter.</td>
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<tr>
<td>2. Submission Summary Sheet.</td>
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<tr>
<td>3. Evidence of approval from Health Canada, including:</td>
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<tr>
<td>- a copy of the Notice of Compliance (NOC),</td>
</tr>
<tr>
<td>- a copy of the completed Drug Notification Form (DNF) dated and signed, and</td>
</tr>
<tr>
<td>- a copy of the Product Monograph (PM).</td>
</tr>
<tr>
<td>4. Matching control number on the original NOC, most recent NOC, CPID or DNF issued by Health Canada.</td>
</tr>
<tr>
<td>5. Unrestricted letter of consent permitting the ministry to exchange information about the product with Health Canada, other Canadian provinces and territories, the Canadian Agency for Drugs and Technologies in Health (CADTH), the Patented Medicine Prices Review Board (PMPRB) and Cancer Care Ontario (CCO).</td>
</tr>
<tr>
<td>6. Proposed drug benefit price, including all dosage forms, strengths and package</td>
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7. Evidence that the manufacturer is able to supply the product at the proposed drug benefit price in a quantity sufficient to meet the anticipated demand for the product.

8. Evidence of formulation proportionality (CPID) and/or bioequivalence study for additional strengths or package sizes.

9. Letter confirming third party manufacturer involvement, if applicable.

10. Business agreement letters from all parties involved to cross reference product files, as applicable.

11. Confirmation whether the cross-referenced manufacturer has filed information with Health Canada, if applicable.

12. Certification that no rebates were provided to a person listed under subsection 11.5(1) of the ODBA since Health Canada approved the product for sale in Canada.

13. Confirmation that the clinical test lot(s) has the same formulation as the commercial lot.

14. Pharmacoeconomic Information:
   a. Pharmacoeconomic Analysis Summary Sheet
### (ODBA) SINGLE SOURCE (ORIGINAL) PRODUCTS, LINE EXTENSIONS, NEW INDICATIONS
(i.e., BENEFIT)

- b. Pharmacoeconomic Analysis (report and model)
- c. Pharmacoeconomic Analysis Work Sheet (waived for CDR and pCODR products)

15. Estimate of the net costs to the Ontario Drug Benefit Program in a three-year period.
   - a. Budget Impact Analysis (report and model; must include an estimate of the net costs to the Ontario Drug Benefit Program in a three-year period)
   - b. ODB Financial Impact Analysis Summary Sheet
   - c. ODB Financial Impact Analysis- assumptions and estimates

16. Product-specific clinical studies and, if available, other clinical evidence of the product’s therapeutic effectiveness or efficacy and of the product’s safety, including any information that relates to adverse drug reactions and any existing clinical studies comparing the product’s therapeutic effectiveness or efficacy and the product safety to that of other products or treatments.

17. Clinical Data Checklist (waived for CDR and pCODR products).

18. Copies of published trials or of trials accepted for publication in peer reviewed literature on therapeutic use, efficacy, safety and adverse effects.

19. Complete listing of published and unpublished studies

20. If requested, the manufacturer must provide written confirmation from the CDR / pCODR Directorate that the drug product is not eligible for review under the CDR / pCODR procedure.

21. Certification confirming Product is not a private label product.
DIDFA SUBMISSION REQUIREMENTS FOR MULTIPLE SOURCE INTERCHANGEABLE LISTED DRUG PRODUCTS
(i.e., A BENEFIT)

1. Cover Letter.

2. Submission Summary Sheet.

3. Evidence of approval from Health Canada, including:
   - a copy of the Notice of Compliance (NOC) and/or No Objection Letter (NOL),
   - a copy of the completed Drug Notification Form (DNF) dated and signed, and
   - a copy of the Product Monograph (PM).

4. Matching control number on the original NOC, most recent NOC, CPID or DNF issued by Health Canada.

5. Unrestricted letter of consent permitting the ministry to exchange information about the product with Health Canada, other Canadian provinces and territories, Canadian Agency for Drugs and Technologies in Health (CADTH), the Patented Medicines Prices Review Board (PMPRB), and Cancer Care Ontario (CCO).

6. Certified Product Identification Document (CPID) or Master Formula.

7. Proposed drug benefit price, including all dosage forms and strengths and package sizes.

8. Evidence that the manufacturer is able to supply the product at the proposed drug benefit price in a quantity sufficient to meet the anticipated demand for the product.

9. Evidence of formulation proportionality (CPID) and/or bioequivalence study for additional strengths or package sizes.
10. Letter confirming third party manufacturer involvement, if applicable.

11. Confirmation whether the cross-referenced manufacturer has filed information with Health Canada, if applicable.

12. Certification that no rebates were provided to a person listed under subsection 12.1(1) of the DIDFA since Health Canada approved the product for sale in Canada.

13. Product confirmation letter from the manufacturer of the cross-reference products and the submitted product, as applicable.

14. Business agreement letters from all parties involved to cross reference product files, as applicable.

15. Letter confirming no patent infringement.

16. Indicate if a Non Canadian Reference Product (NCRP) is used and for a non-streamlined drug product, provide justification for its use.

17. Product specific 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/innovator product, if applicable.

18. Product specific comparative pharmaceutical equivalence data that will show the
### DIDFA SUBMISSION REQUIREMENTS FOR MULTIPLE SOURCE INTERCHANGEABLE LISTED DRUG PRODUCTS
(i.e., A BENEFIT)

- interchangeability of the product with the original/innovator product, if applicable.

19. Certification confirming Product is not a private label product.

### OFI SUBMISSION REQUIREMENTS FOR INTERCHANGEABLE DRUG PRODUCTS
(i.e., NOT A BENEFIT)

1. Cover Letter.

2. Submission Summary Sheet.

3. Evidence of approval from Health Canada, including:
   - a copy of the Notice of Compliance (NOC) and/or No Objection Letter (NOL),
   - a copy of the completed Drug Notification Form (DNF) dated and signed, and
   - a copy of the Product Monograph (PM).

4. Matching control number on the original NOC, most recent NOC, CPID or DNF issued by Health Canada.

5. Unrestricted letter of consent permitting the ministry to exchange information about the product with Health Canada, other Canadian provinces and territories, Canadian Agency for Drugs and Technologies in Health (CADTH), the Patented Medicines Prices Review Board (PMPRB), and Cancer Care Ontario (CCO).

6. Certified Product Identification Document (CPID) or Master Formula.
<table>
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<th>OFI SUBMISSION REQUIREMENTS FOR INTERCHANGEABLE DRUG PRODUCTS (i.e., NOT A BENEFIT)</th>
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<tr>
<td>7.</td>
<td>Manufacturer’s List Price, including all dosage forms and strengths and package sizes.</td>
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<tr>
<td>8.</td>
<td>Evidence of formulation proportionality (CPID) and/or bioequivalence study for additional strengths or package sizes.</td>
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<tr>
<td>9.</td>
<td>Letter confirming third party manufacturer involvement, if applicable.</td>
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<tr>
<td>10.</td>
<td>Confirmation whether the cross-referenced manufacturer has filed information with Health Canada, if applicable.</td>
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<tr>
<td>11.</td>
<td>Certification that no rebates were provided to a person listed under subsection 12.1(1) of the DIDFA since Health Canada approved the product for sale in Canada.</td>
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<td>12.</td>
<td>Product confirmation letter from the manufacturer of the cross-reference products and the submitted product, as applicable.</td>
</tr>
<tr>
<td>13.</td>
<td>Business agreement letters from all parties involved to cross reference product files, as applicable.</td>
</tr>
<tr>
<td>14.</td>
<td>Letter confirming no patent infringement.</td>
</tr>
<tr>
<td>15.</td>
<td>Indicate if a Non Canadian Reference Product (NCRP) is used, manufacturers must provide justification and the necessary requirements set out in the guidelines.</td>
</tr>
</tbody>
</table>
OFI SUBMISSION REQUIREMENTS FOR INTERCHANGEABLE DRUG PRODUCTS
(i.e., NOT A BENEFIT)

16. Reference Product Requirements:
   (i) Drug Identification Number (DIN);
   (ii) Brand Name;
   (iii) Full Chemical name (molecule);
   (iv) Strength;
   (v) Dosage Form;
   (vi) Original Manufacturer Name; and
   (vii) A copy of summary of bioequivalence study final report between the submitted and reference drug products for oral solid dosage forms, non-aqueous, oil-based solutions, suspension and metered dose inhalers. The study final report must contain the product name, generic name, lot number and expiry date of the submitted and reference products.

When the lot number and expiry date may not be found in the study final report, please submit both the bioequivalence study final report and the summary or synopsis of the bioequivalence study so that the required information for item number 7 of the Implementation of Off-Formulary Interchangeability guidance is provided to the ministry.

For aqueous solutions as classified under the Health Canada Guidance for Industry: Pharmaceutical Quality of Aqueous Solutions, the manufacturer must:

17. Submit a waiver of comparative bioavailability studies for oral solutions, as applicable.

18. Submit a waiver of the requirement to demonstrate in vivo bioequivalence for aqueous solutions;

19. Provide proof of purchase of Canadian reference product;
<table>
<thead>
<tr>
<th>OFI SUBMISSION REQUIREMENTS FOR INTERCHANGEABLE DRUG PRODUCTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i.e., NOT A BENEFIT)</td>
</tr>
<tr>
<td>20. Provide a certificate of analysis, i.e., the results of comparative and non-comparative physiochemical parameter tests with the innovator (reference product) demonstrating pharmaceutical equivalence. This includes product name, strength dosage form and package format (if applicable) and the expiry date of the test and reference product;</td>
</tr>
<tr>
<td>21. Describe any device attributes, as required by Health Canada.</td>
</tr>
<tr>
<td>22. Product specific 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/innovator product, if applicable.</td>
</tr>
<tr>
<td>23. Product specific comparative pharmaceutical equivalence data that will show the interchangeability of the product with the original/innovator product, if applicable.</td>
</tr>
<tr>
<td>24. Certification confirming Product is not a private label product</td>
</tr>
</tbody>
</table>

**NOTE:** The onus is on the manufacturer to provide the ministry with complete and accurate information regarding its submission and to provide all other related or requested documents as necessary.

Please be aware that all submissions with incomplete information will not be further processed. As noted above, if any component of a drug submission is found by the ministry during the screening process to be missing, incomplete, inaccurate, irregular, improperly submitted, or otherwise deficient, the entire submission will be deemed incomplete.

For multiple-source products, an incomplete submission is ineligible for further processing within that monthly review period. The manufacturer will be required to correct the deficiency and must wait until the new submission deadline in the following month before the drug product submission is re-screened.
Please note that the ministry cannot advise manufacturers of the completeness of their submissions prior to their review by the ministry.
PART II
SUBMISSION REVIEW PROCESS
PART II-A.

STEP-BY-STEP PROCESS FOR THE SUBMISSION REVIEW FOR FORMULARY DRUG PRODUCTS
PART II-A.1. FILING OF DRUG SUBMISSIONS

A manufacturer who wishes to have a drug product considered for reimbursement through the ODB program should file a submission with the:

Senior Manager
Drug Benefits Management
Drug Programs Policy and Strategy Branch
Ontario Public Drug Programs
Ministry of Health and Long-Term Care
3rd Floor, 5700 Yonge Street
Toronto, ON M2M 4K5

Communication during the Submission Process

All documentation for drug submissions, correspondence regarding listed drug products or any other drug-related matters, (including program management initiatives), must be directed to the Ontario Public Drug Programs (OPDP) of the ministry, and not to the ministry's expert advisory committee, the Committee to Evaluate Drugs (CED), its Chair, or any members or consultants to the Committee.

Direct approaches (in any form) to CED members, in their capacity as members of the Committee, may be viewed as introducing a conflict of interest and might create an appearance of bias or unfairness on the part of committee members. Although the identities of CED members are in the public domain, the identities of CED reviewers are not revealed and are held in confidence by the ministry.

Direct contact by a manufacturer with a CED member or CED consultants/reviewers may result in a delay in the recommendation for the product in order to ensure no conflict of interest has been introduced.

Questions regarding the status of submissions going through the Common Drug Review (CDR) process should be directed to the CDR Directorate housed within the Canadian Agency for Drugs and Technologies in Health (CADTH).
Questions regarding the status of submissions going through the pan-Canadian Oncology Drug Review (pCODR) process should be directed to the pCODR Directorate housed within the Canadian Agency for Drugs and Technologies in Health (CADTH).

**Written/Verbal Communication**

The ministry acknowledges all submissions received from manufacturers in writing. 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, etc.). It is the manufacturer’s responsibility to keep this information current and accurate. The ministry shall not be responsible for any written correspondence directed to incorrect manufacturer contacts where the ministry has not been notified in writing of current manufacturer contacts.

The manufacturers should direct all submission related issues or inquiries to the Drug Submission Group (DSG) Manager or the Senior Manager of the Drug Benefits Management.

**Submission Conditions Prescribed Under Regulations**

A submission must meet the conditions prescribed under O. Reg. 201/96 made under the *Ontario Drug Benefit Act (ODBA)* for single-source products, or the conditions prescribed under Regulation 935 made under the *Drug Interchangeability and Dispensing Fee Act (DIDFA)* for multiple source products.

i) A submission for a **single source product** (i.e., a drug product or chemical entity in a particular dosage form, strength and format not already listed on the Formulary) must meet all of the requirements of O. Reg. 201/96 under *ODBA*. A single source product submission includes a request to:

- list a new chemical entity drug product on the Formulary
- list a product reviewed by the Common Drug Review (CDR) or the pan-Canadian Oncology Drug Review (pCODR) on the Formulary;
- add a new strength of a product or a new dosage form to a listed product on the Formulary;

- add a new indication for a listed product on the Formulary;

- relist a single source product which was previously removed from the Formulary as a benefit on the Formulary;

- re-designate a single source product as a benefit, which is currently listed as “Not-a-Benefit” on the Formulary;

- consider reimbursement of a drug product through the Exceptional Access Program (EAP) (Section 16 of ODBA);

- consider reimbursement of a cancer drug product through the New Drug Funding Program (NDFP); and

- consider reimbursement of a new over-the-counter (OTC) product.

ii) A submission for a **multiple source product** (i.e., a different brand of an already listed drug must meet all of the requirements of Regulation 935 under *DIDFA*). A multiple source submission includes a request to:

- designate a new multiple source product as interchangeable with a listed original/innovator product;

- designate a new strength or dosage form as interchangeable with a listed original/innovator product;

- re-designate a multiple source product previously removed from the Formulary as interchangeable with a listed original/innovator product;
• re-designate a multiple source product listed as a drug benefit which is currently listed as “Not-a-Benefit” on the Formulary;

• consider reimbursement of a Natural Health Product (NHP);

• consider reimbursement of a drug under the Special Drugs Program (SDP);

• consider reimbursement of cancer drug product through the New Drug Funding Program (NDFP);

• consider reimbursement of a generic over-the-counter (OTC) product; and

• consider generic product for Off-Formulary Interchangeability (OFI).

All submission requirements must be met in order to initiate the review process. In addition, 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 or CED may request additional information from manufacturers at any time during the screening and/or review process. Manufacturers are encouraged to respond to these requests in a timely manner to avoid delays in the submission review process. Manufacturers are free to withdraw their submission at any time.

Only complete submissions (i.e., those that meet all regulatory requirements under ODBA or DIDFA) are eligible for review and consideration for reimbursement through the ODB program. The date that the ministry deems a submission complete, as well as the type of review (i.e., first or reconsideration), determines the subsequent ranking of the product versus another in the review process and on the CED agenda. The complete submission date refers to the date when the NDSS letter is sent.
Format and Organization of Submissions

The following approach to preparation of submissions is suggested to facilitate the screening and review process:

Cover Letter/Table of Contents

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

- the name of the product, and its active pharmaceutical ingredient(s), strength, and dosage form (including the various package sizes);

- third party business agreements, if applicable;

- the regulation under which the submission is being made (either ODBA or DIDFA);

- for single source products, the type of submission (new chemical entities, CDR, pCODR, NDFP, etc), the type of listing requested (e.g., General Benefit, Limited Use, Exceptional Access etc.);

- for multiple source products, the type of submission (e.g. streamlined, non-streamlined, OFI) and the name of the original/innovator product to which an interchangeability designation is being sought;

- any applicable exemptions being sought (e.g., additional strength, format, solid oral dosage form, pseudogeneric or aqueous solution, non-Canadian reference product, etc); and

- a rapid review (Pre-NOC and Post-NOC) request, if applicable (relevant to single-source ODBA submissions only).
Organization

It is the requirement that a cover letter and a table of contents (TOC) must accompany the submission. A table of contents must be provided in each binder. The submissions are well organized and indexed/tabbed with description. To facilitate review, hard copies must be clearly tabbed according to the relevant section of the requirements in the TOC. Binders must be sturdy, and not overfilled. Individual binders should not be more than 7.2cm (3 inch) width. Double-sided and paginated pages are preferred. The electronic copies (CDs, DVDs or USB keys) must be well organized in the same manner as the hard copies. The submission information must be organized according to the folders and their subsections, unlocked, and allowing the users to extract every piece of information separately. Manufacturer must not provide submission information in one continuous document.

Disorganized or incomplete submissions may be returned at the discretion of the ministry, and at the manufacturer's expense, without prejudice to re-filing.

Template

Please be advised that templates have been developed to assist manufacturers in providing all relevant submission requirements; templates and contents must not be modified by manufacturers. In addition, work sheets, tables and checklists have been developed to ensure that all relevant information is provided. Templates are located in Part VII of the Guidelines, or refer to the ministry’s website for up-to-date copies of these documents.

If a template is altered, the ministry reserves the right to deem the submission incomplete.

Number of Submission Copies

Submissions will be deemed incomplete if the required number of submission copies is not provided as specified below:
**Single Source / ODBA Submissions**

One (1) full hard copy and two (2) electronic copies (CDs, DVDs or USB keys) of the entire submission, and any additional information requested to complete the submission, must be provided for all single source submissions filed in accordance with the requirements of the ODBA Regulation (including CDR, NDFP, pCODR submissions). Same number of hard and electronic copies must be provided for any reconsideration reviews.

Organized and identical information must be submitted in both hard and electronic copies (CDs, DVDs or USB keys) (see above details on organization). A submission will be deemed incomplete if these requirements are not met.

**Multiple Source / DIDFA Submissions**

One (1) full hard copy and one (1) electronic copies (CDs, DVDs or USB keys) of the entire submission, and any additional information requested to complete the submission must be provided for multiple source submissions (ODB and OFI submissions) filed under *Drug Interchangeability and Dispensing Fee Act Reg. 935*, diabetic testing agent submissions, nutritional products and generic NDFP submissions. Same number of hard and electronic copies must be provided for any reconsideration reviews.

Organized and identical information must be submitted in both hard and electronic copies (see above for details on organization). A submission will be deemed incomplete if these requirements are not met.

In order to facilitate the review of more complex products, (where multiple reviewers may be engaged) the ministry may request additional copies of a submission.

**Transparency**

The ministry continues to make efforts to enhance the transparency of the submission process:

- The ministry posts the status of drug submission for single-source (generally brand name) submissions, and complete streamlined multiple-source (generally generic) submissions. Posting of status for other submission types (e.g. non-
streamlined multiple-source submissions) may be considered in the future depending on stakeholder interest and ministry resources. All other confidential information provided by the manufacturer is held in confidence by the ministry.

- The CED’s recommendation and rationale is provided following each completed review to the submitting manufacturer. Technical portions of the CED reviewers’ reports are available upon written request.

- Under subsection 12(7) of O. Reg 201/96 made under the ODBA, the Executive Officer (EO) may require the manufacturer of the product enter into an agreement with the EO that specifies any volume discount or other amount that may be payable by the manufacturer to the Minister of Finance, and shall agree that the EO may make public the following information, and that information only, with respect to the agreement:

  1. the name of the manufacturer,
  2. the subject-matter of the agreement,
  3. the fact of entering into or terminating the agreement.

In support of this transparency initiative, the EO may, in the EO’s sole discretion, state publicly that the EO has entered into a pricing agreement with the Manufacturer that provides savings to the Ontario Drug Benefit Program. The EO will, however, not disclose the pricing amounts as set out in the agreement. The ministry interprets “subject matter of the agreement” as including only the above noted information (the fact of entering into a pricing agreement, the name of the drug, the name of the Manufacturer, and the fact that the agreement generates savings to the Ontario government), not any other content of the agreement.

- The status of submissions, the rationale supporting the CED recommendations and ministry decisions may be made available in response to requests from the public. The ministry may also publish this information for health professionals or the public. The ministry will hold in confidence any confidential information provided by the manufacturer. (Note: any information that is available in the public domain is not considered to be confidential by the ministry.)

- Please also be advised that this policy may limit the ministry’s ability to exempt information contained in a submission in the event that an access request is
Incomplete Submission

If any of the submission documents or materials is found to be deficient in any respect, irrespective of whether the deficiency goes to form or content, the submission request for the proposed listing of the drug product on the Formulary will be deemed incomplete. There are no exceptions for any type of deficiency. The policy will apply to all product submissions and drug product submissions for single source and multiple source products (streamlined and non-streamlined), regardless of whether they are being proposed for an interchangeability and/or a benefit designation on the Formulary or for inclusion on the Off-Formulary Interchangeability (OFI) list. The onus is on the manufacturer to provide the ministry with complete and accurate information regarding the submission to avoid delays in the listing of their products.

An incomplete submission will not enter the review process for funding considerations until all the required information is received and the submission has been deemed complete.

Except for pre-NOC submissions that are undergoing national review processes i.e. pCODR or CDR, an incomplete submission could be automatically withdrawn from the review process if a manufacturer fails to provide all the requested information within 60 calendar days from the issue date of the NDSS. The original submission may be destroyed at that time, without prejudice to refiling.

New Submission Deadline

New submission deadlines for listing of multiple source products on the Formulary and Off-Formulary Interchangeable listings are posted on the ministry’s website and may be applicable depending on the submission type.
PART II-A.2. SCREENING OF DRUG SUBMISSIONS FOR REGULATORY COMPLIANCE

Submission Receipt and Review

Each drug submission is date and time stamped when it is received by the ministry.

Manufacturers may confirm receipt of a submission by calling the Ontario Public Drug Programs of the ministry at (416) 327-8109. Calls should be made by the manufacturer’s primary contact with the ministry.

Single source submissions are screened for regulatory compliance by ministry staff in sequence, according to the date and time of receipt. The targeted time frame for screening is approximately three weeks from the date the submission is received by the ministry. This timeframe may be prolonged during periods of resource or administrative constraints or for particularly complex submissions. Multiple source (ODB and OFI) submissions are processed according to the new submission deadline posted on the ministry’s website.

If a submission satisfies all the regulatory requirements, it is considered to be “complete”. If a submission does not satisfy all the regulatory requirements, the submission is considered to be “incomplete” and will not proceed through the evaluation process.

Additional information may be requested to meet regulatory requirements made under the ODBA and the DIDFA.

New Submission Deadline for ODB Multiple Source Drugs

This date is applicable to streamlined multiple source (generic) submissions that do not require CED review. All streamlined generic submissions must be received by the ministry before 3:30 p.m. on the scheduled date for inclusion in the next monthly multiple source update package going forward for Executive Officer approval.
**Ministry Communication**

Once a submission is screened by the ministry, a Notice of Drug Submission Status (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 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.

When all regulatory requirements are satisfied, a submission is deemed complete and enters the review process.

Any additional, unsolicited documents received from the manufacturer after the submission is deemed complete may delay the review process and may not be forwarded to the CED for consideration.

**Manufacturer’s Response**

All materials submitted to the ministry must be addressed to the Senior Manager, Drug Benefits Management and not directly to the DSG staff.

A manufacturer should make reference to the drug product (product name/generic name/strength/dosage form/package format and size), the master file number 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, except for pre-NOC submissions undergoing national review processes (i.e., CDR or pCODR). For pre-NOC submission received by the ministry undergoing national review processes will have an alternate deadline specified on the NDSS. A manufacturer’s letter accompanying the additional requested information should make reference to the assigned file numbers and refer to the regulatory deficiencies identified in the NDSS.
An incomplete submission will be automatically withdrawn from consideration if a manufacturer fails to provide all the requested information in the NDSS within 60 calendar days from the issue date of the NDSS, except for pre NOC submissions undergoing national review processes (i.e., CDR or pCODR). For pre-NOC submission received by the ministry undergoing national review processes will have an alternate deadline specified on the NDSS. Once an incomplete submission is withdrawn from consideration, it may be destroyed at that time, without prejudice to refiling.

Ministry staff will screen additional information (resulting from an “incomplete” NDSS letter) provided in the same sequence as all other submissions received (i.e., by date and time of receipt). As noted above, the targeted time frame to screen this information is approximately two weeks, subject to resource constraints.

**Streamlined Multiple-Source Submissions under DIDFA**

Please note that the CED no longer reviews the following types of drug products if they have a declaration of equivalence (DoE) with the original product* or another listed drug product with which they would be designated as interchangeable:

- Certain aqueous solutions [see subsections 6(5) and (5.1) of the DIDFA Regulation]
- Solid oral dosage forms for systemic effect [see subsection 6(7) of the DIDFA Regulation]
- Dermatological products that contain one or more glucocorticoids as the only active ingredient or ingredients [see subsection 6(7.1) of the DIDFA Regulation]; and
- A drug product with a transdermal route of administration for systemic effect [see subsection 6(7.2) of the DIDFA Regulation].

*For the definition of “original product”, please refer to subsection 1(1) of the DIDFA Regulation.

Submissions for the drug products described above are considered “streamlined”, as the ministry has harmonized its scientific review of these products with the scientific review by Health Canada.
For streamlined multiple source products, submissions that have been designated as complete by the ministry will be forwarded for approval to the Executive Officer for consideration for inclusion in the next available monthly formulary package. Note that all final listing decisions are made by the Executive Officer.

For additional information, please refer to the DIDFA Regulation, subsections 6(5.1), 6(6) and 6(7), 6(7.1) and 6(7.2).
PART II-A.3. FIRST REVIEW BY THE COMMITTEE TO EVALUATE DRUGS (CED)

Complete submissions undergo review by the ministry’s expert advisory committee, the Committee to Evaluate Drugs (CED). Submissions are reviewed by CED members and/or by reviewers drawn from an extensive roster of external clinical and pharmacoeconomic consultants. The identification of appropriate submission reviewers typically takes two to seven working days. The targeted time frame for the completion of reviews is four weeks.

The CED 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 CED review. See Parts II and III for more information.

When a submission is ready for CED consideration (either due to completion of CED consultant review or release of a final CDEC recommendation), it is scheduled as a First Review agenda item for the next available CED meeting, and ranked in the agenda according to the date the submission was deemed complete by the ministry.

Effective April 1, 2016, all drug products reviewed by the Common Drug Review (CDR) and the pan-Canadian Oncology Drug Review (pCODR) will no longer require a routine review by the Committee to Evaluate Drugs (CED), the ministry’s expert drug advisory committee.

CED Recommendation

The CED discusses each submission, with input from reviewers, other expert external consultants, and the ministry as required.

When reviewing single-source submissions, the CED evaluates the comparative therapeutic efficacy and safety for the patient populations covered by the ODB program, cost-effectiveness in comparison to currently-reimbursed alternatives, patient value or input, and impact on other health services. Overall, this comprehensive evaluation contributes to the determination of value-for-money for the ODB program.
For submissions that have been reviewed through the CDR or pCODR, on a case-by-case basis, the CED will review CDEC or pERC final recommendation in view of the Ontario context, i.e., in light of current Formulary listings, the need for clinical criteria, and the population served by the ODB program.

The CED has a number of options in making a recommendation regarding a product, including:

- General Benefit listing;
- Listing with therapeutic notes or if appropriate, Limited Use;
- Consideration of reimbursement through the Exceptional Access Program (EAP), Section 16 of the ODBA;
  - individual clinical review by an external CED consultant; or
  - internal Branch review according to specific clinical criteria recommended by the CED;
- Facilitated access (FA);
- Special Drugs Program reimbursement (limited to generic brands, strengths, and formats of existing products funded under SDP, as outlined in Part II);
- Cancer drug product reimbursement under NDFP; or
- No reimbursement under any circumstances

Different drug products in the same submission (e.g. different strengths or formats) may be subject to differing recommendations, based on the CED’s assessment.

For complex products, if a recommendation has been made by the CED for listing with criteria, EAP or FA listing, a subcommittee may be asked to develop the clinical criteria. In such cases, additional time may be required prior to final reimbursement criteria being communicated to the manufacturer.

The committee’s recommendations are drafted into minutes which are ratified by the CED at a subsequent meeting of the Committee.
Communication to Manufacturers

A CED recommendation letter is issued to a manufacturer after the CED review. The recommendation letter is generally faxed within three to four weeks after the ratification of the CED minutes. The recommendation letter will summarize the CED’s recommendation and reason(s) for its recommendation.
PART II-A.4. RECONSIDERATIONS BY THE COMMITTEE TO EVALUATE DRUGS (CED)

Manufacturers are offered a nine-month period to respond to a negative CED recommendation. One hard copy and two electronic copies (CDs, DVDs or USB keys) of the response must be provided for single source submissions, and two copies must be provided for multiple source submissions. If a response is received during this time frame, the submission will be reconsidered by the CED, as the agenda permits. If a manufacturer fails to address the outstanding issues within a nine-month time period, the submission may be withdrawn and subsequently destroyed. A full submission is required after the nine-month period has elapsed.

If a manufacturer receives another negative recommendation, they will be offered another nine-month period to respond to the CED’s concerns. Please note that after two reconsiderations, the manufacturer must provide a new submission (i.e., a first review submission) with substantive new clinical or economic data for further consideration by the CED.

Please note that for products that have been reviewed by the CDR process or the pCODR process, manufacturers’ requests for reconsideration must be directed to CDR or pCODR.
PART II-A.5. MEETINGS WITH MANUFACTURERS

A manufacturer may request a meeting with the ministry to discuss any outstanding issues/concerns regarding a submission. Requests for a meeting should be made in writing to the ministry.

Meetings with ministry staff may be requested if a manufacturer remains unclear on the reasons for the CED rejection, or remains uncertain about the necessary steps required to overcome the objections of the CED. Following a meeting, a manufacturer may decide whether to accept a negative recommendation, withdraw the submission, or respond in writing for further CED consideration.

Manufacturers may also request a meeting with the ministry to discuss upcoming or future submissions. Requests for meeting should be made in writing to the ministry. Manufacturers should provide a meeting agenda and meeting materials to the ministry two weeks before a pre-submission meeting.
PART II-A.6. 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 to withdraw a submission. The submission will be returned to the manufacturer at their expense. The manufacturer should include the account number of the courier service in the request letter.

The ministry may also withdraw the submission from the review process if the manufacturer does not sufficiently address:

- regulatory deficiencies identified in the Notice of Drug Submission Status (NDSS) within 60 calendar days of the issue date of the latest NDSS; except for pre-NOC submissions undergoing national review processes (i.e., CDR or pCODR); or
- CED concerns within nine months of the date of a negative recommendation letter.

Submissions that have been withdrawn by the ministry may be destroyed.

Please note that the ministry may retain certain portions of the submission for its records.

NOTE: When a CDR or pCODR submission is withdrawn from the CDR or the pCODR review process, that submission will be withdrawn from the ministry review process automatically.
PART II-A.7. MANUFACTURER INQUIRIES

The ministry acknowledges all submission inquiries or issues made by manufacturers in writing and over the phone. All written and verbal communication between the ministry and a manufacturer takes place through a single primary contact of the manufacturer.

The ministry requires written notification in order to change the primary contact, or any other information related to contact information (e.g., address, telephone number, etc.). It is the manufacturer’s responsibility to keep this information current and accurate. The ministry may deny inquiries from a person who is not registered as a primary contact on the ministry contact list.

In order to manage manufacturer inquiries in a timely manner, the manufacturers should direct all written or verbal submission related inquiries or issues to the Manager, Drug Submissions or the Senior Manager, Drug Benefits Management.
PART II-A.8. TRANSPARENCY OF THE COMMITTEE TO EVALUATE DRUGS (CED) REVIEW PROCESS

In recent years, the ministry has introduced a number of measures to increase the transparency of Ontario’s drug submission review process and to keep stakeholders informed of the recommendations made in respect of drug submissions to the ministry by the Committee to Evaluate Drugs (CED).

Summaries of the recommendations made by the CED to the Executive Officer (EO) of Ontario Public Drug Programs may be posted on the ministry’s website. This enables interested members of industry and the public to not only monitor the status of drug submissions as they proceed through the Ontario Drug Benefit (ODB) review process but also to review the reasons underlying the CED recommendations.

Please note as a consequence of this transparency initiative, certain information provided by manufacturers in their submissions may be made public, as described elsewhere in the Guidelines. This policy may therefore limit the ministry’s ability to exempt information contained in a submission in the event that an access request is made for that information under the Freedom of Information and Protection of Privacy Act.

The CED recommendations and reasons posted on the ministry’s website outline:

- details of the CED’s recommendations and their supporting rationale compared to currently available alternatives;
- a discussion of clinical studies;
- reference to alternative medications available under the Ontario Public Drug Programs;
- information on cost-effectiveness and/or cost comparisons to alternatives; and
- the EO’s final decision and funding status.

Information that may be included:
- comparative analyses regarding the efficacy, safety, price, and cost-effectiveness of submitted drug products versus alternatives;
- published information; and
- budget impact.

Information that will not be included:

- unpublished data/information submitted by manufacturers in confidence that is not otherwise available in the public domain;
- detailed budget impact analyses submitted by manufacturers;
- details of manufacturer’s agreements with the ministry. Commercial prices will be published as appropriate; and
- medical diagnosis, symptom assessment, health counselling, and medical opinions/advice for individuals.
PART II-A.9. CHALLENGE OF INTERCHANGEABILITY PROCESS

Challenges to a Competitor’s Product

A “challenge” refers to information submitted to the ministry disputing a competitor’s submission or product listing e.g. interchangeability designation, efficacy and safety issue etc.

Challenges to Multiple-Source Streamlined Submissions

The ministry has harmonized its scientific review of multiple-source products with that of Health Canada for the majority of multi-source submissions (e.g., solid oral dosage forms for systemic effect, dermatological products that contain one or more glucocorticoids as the only active ingredient(s), transdermal products for systemic effect and certain types of aqueous solutions) where Health Canada has declared the product as equivalent to the original/innovator product or another listed interchangeable product (refer to subsections 6(5), (5.1), (7), (7.1) and (7.2) of Regulation 935 made under the DIDFA). For these “streamlined” submissions, the ministry does not conduct its own review of the bioequivalence or pharmaceutical equivalence data; therefore, the ministry will generally not consider challenges for these products. Information and concerns related to the bioequivalence or pharmaceutical equivalence of these “streamlined” products should be forwarded to Health Canada for consideration. The ministry will not consider any challenges to a “streamlined” submission until confirmation is received that Health Canada has first been engaged and has accepted consideration of the challenge.

For further details on streamlined multiple-source submissions, please refer to subsections 6(1) to (7.2) of Reg. 935 made under the DIDFA.

Challenges to Non-Streamlined (single source and multiple-Source) Submissions

The ministry may accept challenges against single-source and non-streamlined multiple-source products provided that the submissions associated with the products being challenged have been received by the ministry and are deemed complete.
All challenges must be clearly documented and provided in writing to the ministry. Verbal concerns from manufacturers will not be considered by the ministry, nor brought forward to the CED for consideration.

In general, the CED will consider **ONLY ONE** challenge for a given product per submitter based on first challenge information received by the ministry. Please ensure all relevant information is included in that challenge submission, as any additional data subsequently submitted to the ministry will not be considered. Any manufacturer challenge accepted will expire one year from date of receipt, if accepted by the ministry for review.

One hard copy and two electronic copies (CDs, DVDs or USB keys) of the entire challenge should be supplied to the ministry. Any information provided by a manufacturer regarding a competitor's product will be shared in whole or in part with the competitor for their consideration and comments, at the discretion of the ministry and without further notification of the challenging manufacturer by the ministry.

Other than providing an acknowledgement of receipt, the ministry will not communicate further about the status of a challenge or of the competitor’s submission or listing status until a decision or recommendation has been made by the CED and the Executive Officer (EO). The ministry will inform the manufacturer in writing on the CED recommendation and EO’s final decision.
PART II-A.10. 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.

Non-CDR, non-pCODR submissions and Non-Streamlined submissions under ODBA

<table>
<thead>
<tr>
<th>Ontario Public Drug Programs Activities</th>
<th>Targeted Time-frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ministry screening of submission</td>
<td>Three weeks (may be longer for complex submissions)</td>
</tr>
<tr>
<td>Reviewer identified for complete submission</td>
<td>Two to seven business days</td>
</tr>
<tr>
<td>Expert review of submission</td>
<td>Four weeks</td>
</tr>
<tr>
<td>For first review submission CED review and recommendation</td>
<td>Two to four months from the date a submission is deemed complete (may be longer for complex submissions)</td>
</tr>
<tr>
<td>For reconsideration review submission CED review and recommendation</td>
<td>As CED agenda permits</td>
</tr>
<tr>
<td>Notice of final acceptance (OPDP Notice) – for positive listing decisions</td>
<td>Approximately seven business days prior to the effective Formulary/CDI listing date</td>
</tr>
<tr>
<td>Ontario Public Drug Programs Activities</td>
<td>Targeted Time-frame</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Ministry screening of submission</td>
<td>Three weeks, initiated upon receipt of a complete CDR or pCODR submission (may be longer for complex submissions)</td>
</tr>
<tr>
<td>CED review and recommendation</td>
<td>Less than two months after CDEC’s or pERC’s Final Recommendation is released</td>
</tr>
<tr>
<td>Notice of final acceptance (OPDP Notice) – for positive listing decisions</td>
<td>Approximately seven business days prior to the effective Formulary/CDI listing date</td>
</tr>
</tbody>
</table>
### Streamlined submissions under *DIDFA*

<table>
<thead>
<tr>
<th>Ontario Public Drug Programs Activities</th>
<th>Targeted Time-frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ministry screening of submission</td>
<td>Submissions received by 3:30 pm on the new submission deadline are screened in one week (ODB-Benefit products) or two weeks (OFI products) from the published new submission deadline.</td>
</tr>
<tr>
<td>Ministry notification of submission status and recommendation, if applicable</td>
<td>NDSS/ recommendation 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. Incomplete submissions will not be considered for that month’s update. Response required within one business day if drug data (DIN/price) is incorrect. Otherwise, no response required.</td>
</tr>
<tr>
<td>Notice of final acceptance (OPDP Notice) – for positive listing decisions</td>
<td>Approximately seven business days prior to the effective Formulary/CDI listing date, and approximately 7 weeks after the NDSS letter is issued (dependant on EO approval).</td>
</tr>
</tbody>
</table>
Non-Streamlined submissions under *DIDFA*

<table>
<thead>
<tr>
<th>Ontario Public Drug Programs Activities</th>
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</thead>
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<tr>
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</tr>
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<td>Ministry notification of submission status and recommendation, if applicable</td>
<td>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</td>
</tr>
<tr>
<td>Reviewer identified for complete submission</td>
<td>Two to seven business days</td>
</tr>
<tr>
<td>Expert review of submission</td>
<td>Four weeks</td>
</tr>
<tr>
<td>For first review submission CED review and recommendation</td>
<td>Two to four months from the date a submission is deemed complete (may be longer for complex submissions)</td>
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<tr>
<td>For reconsideration review submission CED review and recommendation</td>
<td>As CED agenda permits</td>
</tr>
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<td>Approximately seven business days prior to the effective Formulary/CDI listing date</td>
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</tbody>
</table>
PART II-B.

PROGRAM POLICIES RELATED TO DRUG SUBMISSIONS EVALUATIONS
PART II-B.1. STREAMLINED MULTIPLE SOURCE DRUG PRODUCT AND LISTING CONSIDERATIONS

The following outlines the process and timelines for Formulary and Off-Formulary Interchangeability (OFI) streamlined multiple source drug products:

1. Oral solid dosage forms for systemic effect, dermatological products that contain one or more glucocorticoids as the only active ingredient(s), transdermal products for systemic effect with a Health Canada declaration of equivalence (DoE) and certain aqueous solutions with a Health Canada declaration of equivalence (DoE) on its Notice of compliance (NOC) dated on/after February 15, 2005 are screened for completeness and recommended by the ministry for listing. These “streamlined” multiple source products are not reviewed by the Committee to Evaluate Drugs (CED).

2. The ministry endeavours to process new Formulary streamlined multiple source submissions (ODB-Benefit products) one week after the monthly new submission deadline cut-off date. For OFI submissions, the ministry endeavours to process streamlined multiple source submissions two weeks after the new submission deadline cut-off date.

3. The ministry screens submissions for compliance with applicable regulatory and policy requirements and issues a Notice of Drug Submission Status (NDSS). The NDSS letters for the Formulary products are usually faxed to the manufacturer by 5 p.m. two weeks after the new submission deadline. The NDSS letter for OFI products is usually faxed by 5 p.m. three weeks after the new submission deadline.

4. Formulary generic products are generally priced at 25% of the listed original/innovator product (typically the brand name product), unless a price exemption set out in the ODBA Regulation applies. Refer to section 11 of the ODBA Regulation and sections 6 and 7 of the DIDFA Regulation in Part III-B.1.h for detail pricing requirements.

5. Manufacturers requesting a new generic drug to be considered for listing on the Ontario Drug Benefit (ODB) Formulary need to submit a Generic Pricing
Confirmation Form to the pan-Canadian Pharmaceutical Alliance (pCPA), as per the Pan-Canadian Generic Value Price Initiative Generic Pricing Framework. If the manufacturer has not done so, please submit the completed form to pCPA immediately. Delays in submitting the form may impact the timing of the product’s listing on the formulary. The price confirmation form and information regarding this process can be found at: http://formulary.drugplan.health.gov.sk.ca/PanCanadian.aspx

With this centralized process, a separate price confirmation step is now in place for streamlined generic product submissions to Ontario that are deemed to be complete and non-streamlined generic product submissions that have received a positive Committee to Evaluate Drugs (CED) recommendation for listing on the Formulary (price confirmation is not done for incomplete submissions or non-streamlined submissions pending review by the CED).

6. Once a manufacturer received a complete NDSS letter, the manufacturers will only be asked to respond to the Branch if the data (product description, DIN or price, etc.) provided in the letter is incorrect. Any changes/clarification must be provided in writing to the Manager, Benefits Administration one business day from the date of the fax. You may wish to fax your written response; however, the original document must also be forwarded to the Branch. If there is no response from the manufacturer, the product(s) will go forward for consideration by the EO with no changes. If the manufacturer responds with a correction in one business day timeframe, the ministry will make the appropriate changes so that the product(s) will go forward for consideration by the EO.

7. Once the product information, price and DIN are confirmed, the submission package is prepared for EO review and approval, approximately 5 to 6 weeks from the new submission deadline. The EO may designate a drug product in the Formulary as a listed drug product or in the OFI listing as an interchangeable product only where the EO considers it to be in the public interest to do so.

8. Following approval by the EO, the Formulary update is published on the ministry website and communicated to industry stakeholders via the electronic OPDP Notice. The effective date of the Formulary is approximately 7 business days following the issue of the OPDP Notices.

9. The entire process for an approved streamlined multiple source drug product takes, from the new submission deadline to the effective date of the Formulary update,
approximately 7 weeks. This excludes the time required for the negotiation of an applicable price exemption.

Note: Formulary products refer to products that are listed as benefit in the Formulary.

OFI products refer to products listed as interchangeable on the OFI listing but are not benefits on the Formulary.
PART II-B.2. NON-STREAMLINED MULTIPLE SOURCE DRUG PRODUCT REVIEW

Non-streamlined multiple source drug products are generally products without declaration of equivalence (DoE) noted on the Notice of Compliance (NOC) issued by Health Canada. The following outlines the process and timelines for Formulary and Off-Formulary Interchangeability (OFI) non-streamlined multiple source drug products:

1. The ministry endeavours to process all new non-streamlined multiple source Formulary submissions one week after the cut-off date of the monthly new submission deadline. For OFI submissions, the ministry endeavours to process non-streamlined multiple source submissions two weeks after the cut-off date of new submission deadline.

2. The ministry screens submissions for compliance with applicable regulatory and policy requirements and issues a Notice of Drug Submission Status (NDSS). The NDSS letters for the Formulary products are usually faxed to the manufacturer by 5 p.m. two weeks after the new submission Deadline. The NDSS letter for OFI products is usually faxed by 5 p.m. three weeks after the new submission deadline.

3. The complete submission is sent to a CED reviewer who reviews the submission and prepares a written report. This only occurs once the submission has met all regulatory requirements and is deemed complete. It generally takes four weeks for the reviewer to complete his/her report.

4. The reviewer report is forwarded to the CED for presentation at the next scheduled CED meeting. The CED generally meets once monthly, on the 2nd Wednesday of the month. Minutes from the CED meeting are prepared and circulated to members to be ratified at the following CED meeting.

5. Letters detailing the CED recommendations are prepared by ministry staff and sent to the manufacturers by fax.

6. Manufacturers requesting a new generic drug to be considered for listing on the Ontario Drug Benefit (ODB) Formulary need to submit a Generic Pricing Confirmation Form to the pan-Canadian Pharmaceutical Alliance (pCPA), as per the Pan-Canadian Generic Value Price Initiative Generic Pricing Framework. If the
manufacturer has not done so, please submit the completed form to pCPA immediately. Delays in submitting the form may impact the timing of the product’s listing on the formulary. The price confirmation form and information regarding this process can be found at:
http://formulary.drugplan.health.gov.sk.ca/PanCanadian.aspx

With this centralized process, a separate price confirmation step is now in place for streamlined generic product submissions to Ontario that are deemed to be complete and non-streamlined generic product submissions that have received a positive Committee to Evaluate Drugs (CED) recommendation for listing on the Formulary (price confirmation is not done for incomplete submissions or non-streamlined submissions pending review by the CED).

7. Where the CED has made a positive listing recommendation, the manufacturers will only be asked to respond to the Branch if the data (product description, DIN or price, etc.) provided in the letter is incorrect. Any changes/clarification must be provided in writing to the Manager, Benefits Administration one business day from the date of the fax. You may wish to fax your written response; however, the original document must also be forwarded to the Branch. If there is no response from the manufacturer, the product(s) will go forward for consideration by the EO with no changes. If the manufacturer responds with a correction in one business day timeframe, the ministry will make the appropriate changes so that the product(s) will go forward for consideration by the EO.

8. Once the price and DIN are confirmed, the products are included in the submission package prepared for the EO’s review and approval. The EO may designate a drug product in the Formulary as a listed drug product or in the OFI as interchangeable drug product only where the EO considers it to be in the public interest to do so.

9. Formulary generic products are generally priced at 25% of the listed original/innovator product (typically the brand name product), unless a price exemption set out in the ODBA Regulation applies. Refer to Part III-B.1.h for detail pricing requirements.

10. Following approval by the EO, the Formulary update is published on the ministry website and communicated to industry stakeholders via the electronic OPDP Notice. The effective date of the Formulary is approximately 7 business days following the issuance of the OPDP Notices.
11. For approved non-streamlined multiple source drug products, the entire submission review process, from the new submission deadline to the effective date of the Formulary update, takes approximately 16 to 20 weeks. There may also be instances where the time required may exceed 20 weeks in certain circumstances. This excludes the time required to negotiate a price exemption.

Note: Formulary products refer to products that are listed as benefit in the Formulary.

OFI products refer to products listed as interchangeable on the OFI listing but are not benefits on the Formulary.
PART II-B.3. RE-LISTING OF DELISTED DRUG PRODUCTS

If a brand or generic drug product is delisted as a drug benefit, or maintains an interchangeability designation, and it is identified in the Formulary as “Not-a-Benefit”, manufacturers must make a submission to the ministry to have a “Not-a-Benefit” drug product reinstated as a drug benefit.

Manufacturers are encouraged to contact the ministry prior to making a submission to relist a product.

If a manufacturer requests a product to be relisted within one year of its delisting as a benefit, the following minimum submission requirements are required (subject to the discretion of the ministry to request additional information):

1. Cover Letter for each submission;

2. Confirmation that there is no change in the master formulation and that the bioavailability of the product has not been affected (i.e., it is the same product at the time that it was de-listed). The master formulation originally approved for listing and the current master formulation must be provided.

   If there has been any change to the drug product since its previous listing, please clearly identify the change, provide the rationale for the change, and submit the appropriate documentation;

3. Current pricing information, including all dosage forms and strengths, package format and sizes; and

4. Manufacturer’s confirmation of their ability to supply product for the anticipated demand.

A new full submission is required when a drug product has been “not-a-benefit” more than one year or has been delisted altogether from the Formulary due to a Health
Canada Advisory, manufacturer withdrawal from market, or a recommendation to delist the product by the CED, as examples.

Notwithstanding the foregoing, the ministry may, in its sole discretion, request additional documentation at any time that the ministry determines may be necessary for any particular drug submission, and must be satisfied that all regulatory requirements for listing under the ODBA and DIDFA have been met.

Note: For products that are entirely removed from listing on the Formulary, a full submission is required for consideration of relisting.
PART II-B.4. SPECIAL DRUGS PROGRAM (SDP)

The screening and review of SDP submissions will follow the current process as noted in the Guidelines and set out in section 6 of Reg. 935 (DIDFA), subject to any additional requirements as determined by the ministry, where the ministry determines it necessary to properly evaluate the submission.

SDP submissions must comply with the requirements set out in Reg. 935 made under DIDFA and Part – III B of the Submission Guidelines.

A SDP submission will be considered “streamlined” if the drug product is:

- a solid oral dosage form for systemic effect that has been designated by Health Canada as equivalent to an existing drug product funded under SDP;
- a dermatological product that contains one or more glucocorticoids as the only active ingredient(s) that has been designated by Health Canada as equivalent to an existing drug product funded under SDP;
- a transdermal product for systemic effect that has been designated by Health Canada as equivalent to an existing drug product funded under SDP; or
- an aqueous solution described in subsection 6(5), (5.1) of the DIDFA Regulation that has been designated by Health Canada as equivalent to an existing drug product funded under SDP.

Streamlined submissions will be reviewed by the ministry to ensure completeness of information.

All non-streamlined submissions must be reviewed by the CED.

If the EO decides to reimburse a drug product through the SDP, the manufacturer will be required to enter into a SDP agreement with the ministry to establish supply, price, and other relevant terms and conditions, prior to the product being made available under the SDP.

NOTE: The SDP is a hospital based program. DIDFA does not apply to the dispensing of a drug in or by a public hospital to an in-patient or out-patient of the hospital. As a
result, the generic substitution rules in DIDFA do not apply to SDP. Further, products
designated as interchangeable on the OFI list are not automatically eligible for funding
under the SDP.
PART II-B.5. OVER-THE-COUNTER (OTC) DRUG PRODUCTS

The ministry funds some Over-the-Counter (OTC) drug products for eligible recipients under the ODB program. The specific OTC drug products covered by the ODB program are listed in the Formulary.

Single Source OTC Products

The EO may consider the review of a new OTC product on a case-by-case basis, and the product must meet at least one of the following conditions:

- there are no alternatives and lack of access to them could lead to life, limb, or organ threatening disease;
- the product is used in combination with another ODB covered drug product;
- the removal of the OTC product would likely lead patients to switch to other toxic and/or more costly alternatives; or
- it is used to treat a communicable disease with a significant public health impact.

Submissions for new OTC products must comply with the requirements set out in section 12 of the ODBA Regulation.

Multi-Source OTC Products

The CED and the ministry will only consider interchangeability requests for generic brands that have the same strengths, dosage form and formats as EXISTING OTC drug products listed in the Formulary. Please note 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-listed from the Formulary.

Submissions for generic versions of existing OTC products listed on the Formulary must comply with the requirements set out in section 6 of Reg. 935 (DIDFA).
The screening and review of OTC submissions will follow the current process as outlined for in Part II and Part III in the Guidelines.

OFI

The ministry does not consider submissions for OTC products for off-formulary interchangeability assessment and designation.
PART II-B.6. NATURAL HEALTH PRODUCTS (NHP)

The ministry reimburses 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 reimbursed to eligible ODB recipients, provided that they continue to satisfy the requirements set out in the ODBA Regulation.

The ministry will only consider funding a new generic NHP if it is interchangeable with an existing NHP currently listed in the Formulary.

The submission requirements for an interchangeable NHP product seeking to be listed in the Formulary as a benefit are the same as the requirements for an interchangeable drug product. For the complete submission requirements for a proposed NHP product, please refer to the section on Submission Requirements for Multiple Source Products of this Guideline.

Because the manufacturer may not have received a Notice of Compliance for its proposed NHP product, 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.

Be advised that the ministry will NOT consider submissions for NHPs in the following cases:

1. new NHP products not listed on the Formulary; or
2. interchangeability designation with another product which is not currently listed as benefit in the Formulary (i.e. a brand or generic product previously delisted or has a ‘not-a-benefit’ status on the Formulary)

To maintain a product listing, the manufacturer must comply with the regulatory conditions for continued listing. Please refer to the section in Part III-B.3 for complete details.

Please be advised that manufacturers are required to notify the ministry regarding any changes in ownership or changes to the product.

Please refer to the section in Part III-B.5 for the complete requirements.
PART III

DETAILED SUBMISSION REQUIREMENTS FOR SINGLE AND MULTIPLE SOURCE DRUG PRODUCTS (ODBA AND DIDFA)

PART III-A. and PART III-B.
PART III-A.

SUBMISSION REQUIREMENTS FOR SINGLE SOURCE DRUG PRODUCTS
(BRAND DRUG PRODUCTS)

ONTARIO DRUG BENEFIT ACT (ODBA) O.REG. 201/96
Single Source Drug Products

A manufacturer submitting a single source drug product (i.e., a drug product or new chemical entity in a particular dosage form and strength not already listed in the Formulary) for listing consideration as a benefit should refer to this section for the interpretation of O. Reg. 201/96 made under the *Ontario Drug Benefit Act* (ODBA).

This section applies to a request to:

- list a new chemical entity drug product on the Formulary;
- list a CDR- or pCODR-reviewed drug product on the Formulary;
- add a new strength, dosage form, or format of an already listed drug product on the Formulary;
- list a new indication for an already listed drug product on the Formulary;
- relist a single source product which was previously delisted from the Formulary;
- re-designate a single source product that was once listed as a benefit and then became listed as “Not a Benefit” on the Formulary;
- have a cancer drug product reimbursed under NDFP;
- have a drug product reimbursed through the EAP under section 16 of the ODBA; or
- have a single source OTC drug product reimbursed.

**Please Note:** A submission for a single source drug product must meet the regulatory requirements as prescribed in O. Reg. 201/96 made under the ODBA and the policy
requirements as set out below. A submission must include all applicable supporting documentation in order to be deemed complete.

The onus is on the manufacturer to provide the ministry with a submission that is complete and accurate and fully compliant with legislative and policy requirements. The ministry will not assume responsibility for advising manufacturers of the completeness of their submissions prior to ministry screening and review. In addition, please note that the ministry reserves the right to request additional information at any time.

Once the full CED review is completed, including the ratification of the minutes from the CED meeting, the submission review process will be considered complete. All recommendations will be submitted to the EO and are subject to the EO’s review and decisions for inclusion in the next monthly Formulary Update.

Please Note: The ministry’s review of a single source drug submission is comprised of two major stages: (1) submission screening (which results in the issuance of an NDSS letter[s]) and (2) CED review (which results in the issuance of a CED recommendation letter). The date of the complete NDSS letter determines the ranking of the product versus another in the CED review process. The date of the CED recommendation letter sent to the manufacturer marks the completion of the CED review process.
PART III-A.1. REQUIREMENTS FOR SINGLE SOURCE DRUG PRODUCT SUBMISSIONS

a. Submission Summary

Every submission must include a copy of the completed Submission Summary. A template has been developed to assist manufacturers in providing all relevant submission requirements. In addition, various template letters, worksheets, tables and summaries have been developed to ensure that all relevant information is provided.

Manufacturers must follow the format and content of these template letters, worksheets, tables and summaries. If there are any conflicts or discrepancies between the requirements set out in these documents and the regulations under the ODBA and the DIDFA, the regulations prevail.

If a template is altered, the ministry reserves the right to deem the submission incomplete.

Templates are located in Part VII of the Guidelines. Refer to the Ministry’s website for current copies of these documents:


b. Cover Letter

The manufacturer must provide a cover letter for each submission and ensure that the following information is included in the cover letter:

- The product name, generic name, strength, dosage form (including the various package sizes) to be considered for reimbursement consideration;

- The letter should include a subject heading that adheres to the following format:
Re: <insert product name/generic name, strength, dosage form, product format and package size> (the “Product”) manufactured by <insert name of manufacturer> (“the Manufacturer”); and ministry-assigned Master File No. and Product File No., if applicable.

- Description of any business agreements or arrangements with any third party (e.g., consultant, cross-licensing manufacturer, co-marketing manufacturer, etc.), if applicable (specify if the third party has filed information with Health Canada);

- Reference to the regulation under which the submission is being made (i.e., ODBA Regulation);

- Full description of the submission proposed for review (e.g., pre-NOC, new chemical, CDR, pCODR, new format, new strength, new indication, etc.);

- The program under which listing is proposed (e.g., ODB, NDFP, EAP, etc.);

- Any applicable exemptions being sought (e.g., additional strength, format, etc.);

- A rapid review (Pre-NOC and Post-NOC) request, if applicable;

- Reference to evidence of bioequivalence where different dosage forms are submitted;

- Reference to evidence of bioequivalence where there is a major difference in formulation proportionality;

- Reference to subsection 12(4) for multiple source product for single source listing, etc., if applicable;
• Reference to evidence of pharmaceutical equivalence for aqueous solutions, if applicable; and

• Certification confirming Product is not a private label product.

c. **Evidence of approval from Health Canada**

12(1) A strength and dosage form of a drug product shall not be designated as a listed drug product unless the manufacturer of the drug product submits to the executive officer,

(a) either,

(i) evidence that Health Canada has approved the product for sale in Canada, a copy of the product’s drug notification form issued by Health Canada and, subject to subsection (2), a copy of the product monograph approved by Health Canada, or

(ii) evidence that an application has been made to Health Canada to approve the product for sale in Canada, and evidence satisfactory to a panel of experts established for the purpose that the product meets at least one of the following criteria:

A. The product is a new chemical entity that is effective for the treatment of an immediately life-threatening disease or other serious disease for which it offers substantial improvements on significant outcomes, including improved efficacy, safety and tolerability and quality of life over other available drug therapies in Canada, or for which no treatment or no other effective drug therapy is currently available in Canada.

B. The product is a new chemical entity that would have, if designated as a listed drug product, the effect of saving or creating efficiencies for the Government of Ontario, an average of at least $2,500,000 per year for the first three years the product is marketed in Ontario.

C. The product is a new chemical entity that would have, if designated as a listed drug product, the effect of saving the Ontario Drug Benefit Program an average of at least $250,000 per year for the first three years the product is marketed in Ontario;
Paragraph (i) of clause 12(1) (a) – Evidence that Health Canada has approved the drug for sale in Canada, DNF and Product Monograph

The ministry requires evidence that Health Canada has considered the efficacy, safety and quality of a drug product and has approved it for sale in Canada. The following documents will be accepted as evidence of approval by Health Canada:

- Notice of Compliance (NOC);
- Completed Drug Notification Form (DNF), dated and signed; and
- Product Monograph approved by Health Canada.

Paragraph (ii) of clause 12(1) (a) – Rapid Review Criteria

A manufacturer of a drug product may submit its drug product for designation as a listed drug product even though Health Canada has not yet approved the product for sale in Canada, if the manufacturer has made an application to Health Canada for approval and a panel of experts is satisfied that the product is a new chemical entity that meets at least one of the following criteria:

A. effective for the treatment of an immediately life-threatening disease or other serious disease for which it offers substantial improvements on significant outcomes compared to other available drug therapies in Canada, or for which no treatment or other effective drug therapy is currently available in Canada; or

B. offer savings or create efficiencies for the Ontario government of at least $2.5M per year for the first three years the product is marketed in Ontario; or

C. offer savings to the Ontario Drug Benefit Program of at least $250,000 per year for the first three years the product is marketed in Ontario.

This allows the ministry to review a product prior to it receiving an NOC from Health Canada so that a positive reimbursement decision may be implemented shortly after the product receives its NOC and is available on the Canadian market.
**Please Note:** A product undergoing this “rapid review” process may not be designated as a listed drug product unless the Executive Officer receives: evidence that Health Canada has approved the product for sale in Canada; a completed, dated and signed drug notification form; and a copy of the product monograph approved by Health Canada, if applicable (see subsection 12(8) of the ODBA Regulation). If a product has undergone rapid review, but still lacks an NOC, DNF and product monograph, a decision on whether or not to list the drug product on the Formulary will not be made, and the decision will be delayed until the required evidence and documents are provided.

Please note that this clause is only applicable for new chemical entities.

12(8) Despite subclause (1) (a) (ii), but subject to subsection (6), a product may not be designated as a listed drug product until evidence that satisfies subclause (1) (a) (i) is also received.

**Notice of Compliance and Drug Notification Form**

The ministry requires a copy of the original NOC (with DIN(s)) and the Health Canada-approved NOC related to the submission, as well as the most recent Product Monograph with matching control number and the date of revision.

If a drug product was/is approved without an NOC (i.e., “old” drugs), only the DNF is required. The DNF should be completed, dated and signed by a senior company official. Post-dated DNFs will not be accepted as complete.

A Notice of Compliance with Conditions (NOC/c) is accepted and considered as a NOC by the ministry. However, the manufacturer must submit a copy of the conditions of approval and the agreed plan with Health Canada, and specify how the condition(s) will be addressed and the approximate timeline for satisfying the conditions, where available. The manufacturer must submit a copy of the updated NOC to the ministry when approved by Health Canada to complete file information.
**Product Monograph**

The submitted Product Monograph must include a product monograph cover page. The cover page must list the control number, approval date, company name and product name, which corresponds to the NOC related to the submission.

A manufacturer must also submit the most recent Product Monograph (if different from the product monograph noted above), with control number, the date of revision, and tracked changes (as well as evidence that Health Canada has approved the changes [i.e., No Objection Letter, Supplemental NOC, etc.]).

**Of Note:** If Health Canada did not approve a product monograph (e.g., “old” drugs), the manufacturer should submit the information generally included in the product monograph, as described in subsection 12(2) of Reg. 201/96 under the ODBA. Refer to the Therapeutic Products Directorate’s Common Technical Document: Product Monograph for further detail.

d. Third Party Involvement

The manufacturer named on the Notice of Compliance (NOC) or Drug Notification Form (DNF) who is responsible for the product in Canada may file a submission with the ministry. It is possible that a party other than the manufacturer named on the NOC or DNF may file a submission. It is also possible that a third party may be involved with a submission in other ways (e.g., product fabrication, or product marketing). Where the third party assumes the right to distribute and sell a drug, they will be considered to assume responsibility for the product and certain confirmations will be necessary from that third party. Where the third party acts as an agent only, on behalf the NOC holder, all of the confirmatory documentation will be required from the NOC holder.

Under these circumstances, additional documentation will be necessary to clearly establish the relationship of the third party with the holder of the NOC, the relationship between any different drug products referred to in the submission, and to ensure that all requirements are met. The submission will not be deemed complete unless sufficient documentation of all aspects of the submission and the relationships between all parties and drug products are provided and well understood. The Formulary/CDI will list the name of the manufacturer holding the NOC.
When a third party is involved in a submission, the following documentation should be provided:

- **Third Party Authorization/Business Agreement** - Where a third party is involved with a submission, a letter should be submitted from both the NOC holder and the third party confirming the business arrangement between the submitting party and the NOC holder. Manufacturers must also identify if the third party has information on file with Health Canada on New Drug Submissions or Abbreviated New Drug Submissions for Subsequent Market-Entry (NDS/ANDS). Depending on the nature of the relationship, the letter from the NOC holder must provide an authorization to the third party to assume responsibility for the submission or authorization to submit the product on the NOC holder's behalf.

- **Notice of Compliance (NOC)** - The NOC from both the NOC holder and the third party (cross-licensed/referenced/importer, etc.) who has information filed with Health Canada is required. The original NOC for cross-referenced products must be submitted. Supplemental NOCs should be submitted as necessary.

- **Consent Letters** - All parties that 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 bodies as outlined in section 12(1)(b) of O. Reg. 201/96 made under the ODBA. If the submission makes reference to another company’s drug product, then the consent letter should be provided by both companies (i.e., both the company filing the submission as well as the actual manufacturer of the drug product). Refer to template letter in Part VII of the Guidelines.

- **Product Confirmation Letter** - A letter from both the NOC holder and the third party who has information filed with Health Canada, dated and signed by a senior company official confirming that the submitted drug product is identical in chemistry and manufacturing, except for labelling and embossing/markings, to the drug product approved on the NOC and to the drug product studied in the bioavailability studies. Refer to template letter in Part VII of the Guidelines.

- **Proposed Drug Benefit Price** - The NOC holder or the third party which holds the rights to sell the submitted product in Canada must provide the proposed
Drug Benefit Price as required in section 6(1) (d) of Reg. 935 or section 12(1)(d) of O. Reg. 201/96.

- **Ability to Supply** - The NOC holder or the third party that holds the rights to sell the submitted product in Canada must also confirm their ability to supply the product as required in section 6 (1)(e) of Reg. 935 or section 12(1)(e) of O. Reg. 201/96. Refer to template letter in Part VII of the Guidelines.

- **Confirmation of Providing No Rebate Letter** - The NOC holder or the third party that holds the rights to sell the submitted product in Canada must certify in writing that no rebates were provided to persons listed under subsection 11.5(1) of the ODBA with respect to the drug product from the time that Health Canada approved the product for sale in Canada. Refer to template letter in Part VII of the Guidelines.

- **Certification Confirming Product is Not a Private Label Product** - The NOC holder must provide a letter certifying that the submitted drug product is not a private label product. Refer to template letter in Part VII of the Guidelines.

e. **Consent Letter**

As federal and provincial governments work to harmonize their drug review processes, it is important for the ministry to be able to communicate freely with other regulatory and review agencies. To satisfy this need, manufacturers are required to submit a letter authorizing the ministry to access all product information filed with Health Canada, other provincial/territorial governments, the Patented Medicine Prices Review Board (PMPRB), the Canadian Agency for Drugs and Technologies in Health (CADTH), other parties or entities involved in the CDR procedure, and authorizing the ministry to disclose any product information in the possession of the ministry to such governments, agencies and bodies.
12(1)(b) A strength and dosage form of a drug product shall not be designated as a listed drug product unless the manufacturer of the drug product submits to the executive officer, a letter authorizing the executive officer to gain access to all information with respect to the product in the possession of Health Canada, the Patented Medicine Prices Review Board established under section 91 of the Patent Act (Canada), 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 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;

Letters should be:

- from the holder of the NOC; and
- dated and signed by a senior company official; and
- free of any restrictive clause(s).

Only letters free of any restriction will be accepted. The letter should authorize the ministry to access any information pertaining to the drug product at any time. Manufacturers must not include restrictions or limitations, such as requiring the notification of the manufacturer before obtaining information from Health Canada, having a representative of the manufacturer present when the ministry obtains information, and/or restricting access to a particular Health Canada submission number. A letter with any restriction will not satisfy this requirement, and the submission will be deemed incomplete.

The ministry’s template letter is provided on the ministry’s website at:

All letters must be prepared using the appropriate manufacturer’s letterhead, dated and signed by the senior company official.
f. **Product Confirmation Letter**

For cross-licensed products, a product confirmation letter from the NOC holder and the other licensee is required.

To assist manufacturers, the ministry has developed a template letter, which is included in Part VII of the Guidelines and on the ministry’s website at:


All letters must be prepared using the appropriate manufacturer’s letterhead, dated and signed by the senior company official.

g. **Proposed Drug Benefit Price**

The manufacturer must submit a proposed drug benefit price (DBP) as prescribed in clause 12(1) (d) of O. Reg. 201/96 under the ODBA.

> 12(1)(d) A strength and dosage form of a drug product shall not be designated as a listed drug product unless the manufacturer of the drug product submits to the executive officer, the proposed drug benefit price of the product;

This requirement must be met for all ODBA (single source) submissions and to comply with Ontario regulatory requirements.

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.).
When the manufacturer is seeking listing for more than one package size, typically for injectable or solutions (e.g., 2 mg/5 mL prefilled syringe, 10 mL and 30 mL vials), the submission must include the proposed DBP for each package size expressed to four decimal places.

**NDFP Submissions:**

In addition to the above, the proposed DBP per mg is required for all submissions for NDFP funding considerations.

**h. Evidence Confirming Ability to Supply**

Where it is proposed that the product be designated as a listed drug product in the Formulary, the manufacturer must be able to supply the drug product at the submitted price in a quantity sufficient to meet the anticipated demand in Ontario.

12(1)(e) A strength and dosage form of a drug product shall not be designated as a listed drug product unless the manufacturer of the drug product submits to the executive officer, evidence that the manufacturer is able to supply the product at the proposed drug benefit price in a quantity sufficient to meet the anticipated demand for the product;

In order to satisfy this requirement, the manufacturer must submit a confirmation letter without any restrictions or limitations.

To assist manufacturers, the ministry has developed a template letter, which is included in Part VII of the Guidelines and on the ministry’s website at:


Submissions will be deemed incomplete when the letter does not adhere to the template format.
All letters must be prepared using the appropriate manufacturer's letterhead, dated and signed by the senior company official.

This requirement must be met for all ODBA (single source) submissions, including CDR and pCODR submissions, to comply with Ontario regulatory requirements.

Please Note:

- This is not required for pre-NOC submissions that have been approved for Rapid Review at the time of submission, but must be supplied within 10 business days of the issuance of the NOC or NOC/c.

- The ministry may request additional documentation to confirm that the manufacturer is able to supply the product at the proposed DBP in a quantity sufficient to meet the anticipated demand for the product.

- It is a condition for an approved drug product to be readily available, and able to supply the Ontario market, at the time the drug is listed in the Formulary. In the event the ministry is notified of inability to supply the drug product at the time of listing or shortly thereafter, the drug product may be removed (delisted) from the Formulary.

i. Letter 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 ODBA with respect to the drug product from the time that Health Canada approved the product for sale in Canada.

12(1)(f) A strength and dosage form of a drug product shall not be designated as a listed drug product unless the manufacturer of the drug product submits to the executive officer, certification in writing that no rebate as defined in subsection 11.5 (15) of the Act has been provided to a person listed in subsection 11.5 (1) of the Act with respect to the product contrary to the Act since Health Canada approved the product for sale in Canada;
Subsection 11.5(15) of the ODBA defines “rebate” as including currency, a discount, refund, trip, free goods or any other prescribed benefit, but not including something provided in accordance with ordinary commercial terms that satisfies the conditions set out in subsection 1(11) of O. Reg. 201/96.

To assist manufacturers, the ministry has developed a template letter which is included in Part VII of the Guidelines and on the ministry’s website at:


All letters must be prepared using the appropriate manufacturer’s letterhead, dated and signed by the senior company official.

j. Clinical Evidence/Studies

A manufacturer must provide copies of published trials or trials accepted for publication in peer reviewed literature on therapeutic use, efficacy, safety and adverse effects.

12(1)(h) A strength and dosage form of a drug product shall not be designated as a listed drug product unless the manufacturer of the drug product submits to the executive officer, clinical studies and, if available, other clinical evidence of the product’s therapeutic effectiveness or efficacy and of the product’s safety, including any information that relates to adverse drug reactions and any existing clinical studies comparing the product’s therapeutic effectiveness or efficacy and the product safety to that of other products or treatments;

Manufacturers may satisfy this requirement by submitting:

- a completed Clinical Data Checklist; and

- clinical evidence, including:
o 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;

o a summary of the critical studies;

o any additional studies completed after the New Drug Submission (NDS) was filed;

o disclosure of all Phase II, III and IV trials and certification of full disclosure by a senior company official; and

  ▪ a complete list of published and unpublished studies.

The submission will be deemed incomplete if any of the above requirements are missing without an adequate explanation.

### Points of Clarification

#### Clinical Data Checklist

The Clinical Data Checklist was developed based on the guidelines that CED reviewers use during their evaluation. It was designed to help manufacturers prepare submissions that are easy to review and ensure submissions proactively address the CED’s questions.

For each question on the Clinical Data Checklist, manufacturers should provide short answers below the question and direct reviewers to the supporting reference page(s). If a question on the Clinical Data Checklist does not apply, please indicate "not applicable" (N/A) on the checklist and provide a rationale if necessary. A copy of the Clinical Data Checklist is available in Part VII of the Guidelines and on the ministry’s website.

The requirement for a Clinical Data Checklist is waived for CDR/pCODR drugs.
Clinical Evidence

In evaluating therapeutic effectiveness and safety, the ministry and the CED place greater reliance on well-designed, comparative clinical trials that answer the clinical questions of interest. Head to head trials, evaluating the submitted drug against relevant comparators, are given the greatest weight.

Please Note: double-blind, randomized, placebo-controlled trials are considered important, but are of lesser importance than head-to-head trials.

Of the data submitted to Health Canada, manufacturers must submit the Comprehensive Summary, or equivalent documentation, relating to the clinical studies of interest. Studies mentioned in the Comprehensive Summary should be cross-referenced to the full study reports and/or manuscripts within the Formulary submission (i.e., full study reports must be provided). Information on Phase 1 studies should be omitted.

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

a. Clinical Overview – Module Section 2.5
b. Summary of Biopharmaceutic Studies and Associated Analytical Methods – Module Section 2.7.1
c. Summary of Clinical Efficacy – Module Section 2.7.3
d. Summary of Clinical Safety – Module Section 2.7.4
e. Tabular Listing of All Clinical Studies – Module Section 5.2

If any of these sections were not a requirement for filing the regulatory submission with Health Canada, please include a statement confirming this on the cover letter of the submission to OPDP.

Should questions arise, it may be necessary to provide further information to establish the linkage information in order to complete a submission.
It is recommended that the clinical data be organized in the following fashion: critical studies and summary (published and unpublished studies that address the key clinical issues); other studies; and supporting documents (e.g., abstracts, consensus statements, review articles, and opinion papers).

Disclosure of all completed or ongoing Phase II, III and IV trials is essential, and should include unpublished studies by other groups or parties known to the manufacturer. Manufacturers should further certify that all known unpublished clinical data has been disclosed. (This information is already required for CDR and pCODR submissions; non-CDR submissions may wish to use the template available at the CADTH website to summarize this data.)

**CPI or Master Formulation of Multiple Strengths**

The NOC for a submitted drug product may contain approval for multiple strengths even though the clinical study with the original test product may have been done on only one of the strengths. In such cases, the approved Certified Product Information Document (CPI) must accompany the submission to provide evidence of formulation proportionality among the various strengths.

**Note:** Where a CPI is not available, the ministry will accept the originally approved master formulation, dated and signed by a Senior Quality Assurance personnel. The master formulation must provide:

- the list of ingredients used to formulate the drug;
- information about the bulk formulation (granulation or liquid), if applicable;
- information about coating ingredients, if applicable; and
- 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.

A summary list of ingredients will not be accepted as a master formulation.
Confirmation of Test Product Formulation

The manufacturer must confirm that the formulation of the test product used in the clinical study is the same as the marketed formulation.

When the test product formulation used in the clinical study is not the current formulation, the manufacturer must provide a CPID or master formulation of the test product and the current product.


Additional Strengths

If a submission includes several strengths of a specific dosage form concurrently, or additional strengths of an already-listed drug product, the manufacturer must refer to subsection 12(3) of O. Reg. 201/96 made under the Ontario Drug Benefit Act to determine if the exemption for additional strengths applies. If the exemption does not apply, the manufacturer must provide clinical studies for each strength of the drug product.

Additional Formats

If a submission includes several formats of a drug product, the manufacturer may be able to rely on clinical data respecting one of the formats. Similarly, if a submission includes a new format of a single source product that is already listed on the Formulary, the manufacturer may be able to rely on clinical data respecting the format already listed.

The manufacturer must refer to subsection 12(3.1) of O. Reg. 201/96 under the Ontario Drug Benefit Act to determine if the exemption for additional formats applies. If the exemption does not apply, the manufacturer must provide clinical studies for each format of the drug product.
Combination Drug Products

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).

- A product-specific study for new combination products is required.

List of Studies

The manufacturer must provide a full list of published and unpublished studies.

| Formatting and Organization |

In order to better guide manufacturers, the following are offered as suggestions to facilitate the CED review of clinical data submitted:

1. The ministry and the CED will balance the therapeutic efficacy, safety and cost-effectiveness of a product with that of suitable alternative agents, where appropriate. Ideally, multiple comparators should be evaluated. A good strategy would be to provide a comparison with the least expensive and the most widely used alternatives. Manufacturers should bear in mind that while one alternative may be a listed benefit, others may be reimbursed through the Exceptional Access mechanism. A higher-priced alternative will be considered for listing if it offers a significant therapeutic advantage. In these instances, a pharmacoeconomic analysis is of critical importance.

2. Any new evidence that was not submitted to Health Canada that may assist the CED in drawing a comparison between the new drug and the listed or alternative products should be submitted.

3. To assist the ministry and the CED in making decisions pertaining to the ODB population, clinical data in relevant patient groups (e.g., elderly, children, etc.) should be submitted.
4. Information on the incidence and descriptions of adverse drug reactions should include data collected from:

- reports on adverse drug reactions and expected/unexpected side effects;
- clinical studies and medical experience; and
- any post-marketing experience conducted by the manufacturer or obtained from prescribing physicians.

5. Very brief summaries are rarely helpful.

6. The CED will consider unpublished data; however, due to the extensive length of some of the study reports, manufacturers are encouraged to prepare unpublished data as they would a publication manuscript.

k. Estimate of Net Costs

A manufacturer must provide an estimate of the net costs to the Ontario Drug Benefit Program in a three-year period as prescribed in clause 12(1)(c) of O. Reg. 201/96 under the ODBA.

12(1)(c) A strength and dosage form of a drug product shall not be designated as a listed drug product unless the manufacturer of the drug product submits to the executive officer, an estimate of the net costs to the Ontario Drug Benefit Program in a three-year period;

A financial impact analysis provides both the ministry and the CED the opportunity to understand the impact of a new drug product on ministry expenditures. The CED considers the analysis, in conjunction with pharmacoeconomic data, in assessing the incremental and overall cost considerations for a new product. The ministry will utilize the analysis when developing ODB expenditure forecasts.
In assessing financial impact, the ministry is interested in yearly expenditures (drug costs only) for the product(s) under consideration. Drug costs should exclude up-charge (mark-up) and dispensing fee. The expenditures should be projected for three consecutive twelve-month periods irrespective of the anticipated date of Formulary listing. Forecasts should be provided for each individual drug product (e.g., strength and dosage form).

The assumptions underlying the forecast should include:

- summary of potential market size, rate of growth, and extrinsic factors that may affect market size;
- initial market capture and how entry impacts existing Formulary product utilization (including the rate of growth/decline of comparators);
- an estimate of the average claim cost and number of claims underlying the forecast; and
- anticipated changes, including generic entry or the entry of new competitor drugs, that may affect market share projections.

The manufacturer should also describe changes in the rate of uptake of the product, projected growth targets, and expected growth in the overall market. In addition, the manufacturer should describe the net effect on other Formulary alternatives.

To assist manufacturers, an ODB Financial Impact Analysis Summary Sheet has been developed; it may be helpful to manufacturers in understanding the factors considered by the ministry in developing expenditure forecasts. A copy of the ODB Financial Impact Analysis Summary Sheet is available in Part VII of the Guidelines and on the ministry’s website.

The use of the template provided by the ministry will facilitate the ministry’s review of submitted forecasts. It is understood that not all of the information in these templates will be available and/or relevant for every product. Where information is not applicable or not available, it should simply be noted as such.

**Note:** The manufacturer must notify the ministry immediately if the price of the submitted drug product changes during the review process, and resubmit any components of the submission affected by the proposed price change (e.g.,
estimate of market penetration or pharmacoeconomic data). Any changes to the submitted price during the review process will require review by the CED.

I. Pharmacoeconomic Evidence and Financial Impact Analysis

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

12(1) (i) A strength and dosage form of a drug product shall not be designated as a listed drug product unless the manufacturer of the drug product submits to the executive officer, evidence demonstrating the benefit of the product in relation to the cost of the product and to alternative products or treatments.

Manufacturers may satisfy this requirement by submitting:

- a completed Pharmacoeconomic Analysis (report and model);
- a completed Pharmacoeconomic Analysis Summary;
- a completed Pharmacoeconomic Analysis Worksheet; and
- Budget Impact Analysis (report and model; must include an estimate of the net costs to the Ontario Drug Benefit Program in a three-year period)
- an ODB Financial Impact Analysis- assumptions and estimates; and

The requirement for a Pharmacoeconomic Analysis Worksheet is waived for CDR and pCODR submissions.
Pharmacoeconomic Analyses

As part of the review of drug submissions, the CED evaluates the value-for-money of new drug product(s), particularly in comparison to alternatives already listed on the ODB Formulary. Pharmacoeconomic analyses provide the CED 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 Summary

As noted above, although not all drug products require a full, detailed analysis, the manufacturer must address the pharmacoeconomic profile of each drug product. In the Pharmacoeconomic Analysis Summary, the manufacturer should indicate whether a detailed economic analysis has been included or justify its absence.

In the Pharmacoeconomic Analysis Summary, the costs of therapy associated with the submitted product and appropriate comparators(s) should be tabulated and the important respective outcomes should be quantified. These are laid out in Sections I, II and III of the sample Pharmacoeconomic Analysis Summary that are available in Part VII of the Guidelines and on the ministry’s website.

The cost of therapy should clearly state the drug, dose, duration, daily cost and cost per usual course. Note that the regimen used for costing should reflect the dose(s) and duration used in clinical trials supporting the efficacy of the product. The cost of comparative therapies should follow a similar process.

It should also be stated if dosing regimens of products in current clinical use differ from the literature (e.g., current clinical practice may be to dose a product twice daily whereas older studies dosed the product three times daily). Comparative therapies may include the lowest cost alternative, most commonly used products based on utilization data, or products recommended in published guidelines. Products other than those listed in the Formulary may be included as comparators of interest.

A concise summary of the relevant comparative clinical outcomes, both measured in clinical trials and extrapolated from models (e.g., success rate, adverse events, deaths, projected survival), is vital to judge the relative value of the therapy and to clearly provide guidance for further economic evaluation.
Pharmacoeconomic Analysis Worksheet

Except for CDR and pCODR submissions, 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. A sample Pharmacoeconomic Analysis Work Sheet is available in Part VII of the Guidelines and on the ministry’s website.
m. Certification Confirming Product is Not a Private Label Product

12.0.2 (1) A drug product that is a private label product shall not be designated as a listed drug product. O. Reg. 220/10, s. 3.

(2) In this section, “private label product” includes a drug product in respect of which,

a) the manufacturer applying for the designation of the product as a listed drug product does not directly fabricate the product itself, and,
   (i) is not controlled by a person that directly fabricates the product, or
   (ii) does not control the person that directly fabricates the product, and

b) either,
   (i) the manufacturer does not have an arm's-length relationship with a wholesaler, an operator of a pharmacy or a company that owns, operates or franchises pharmacies, or
   (ii) the product is to be supplied under a marketing arrangement associating the product with a wholesaler or one or more operators of pharmacies or companies that own, operate or franchise pharmacies. O. Reg 220/10, s. 3.

It is a condition that private label products are not eligible for designation as listed drug products.

The manufacturer must submit a letter confirming that the submitted drug product is not a private label product.

To assist manufacturers, the ministry has developed a template letter which is included in Part VII of the Guidelines and on the ministry’s website at:

PART III-A.2. REQUIREMENTS FOR SPECIFIC CASES
(REGULATORY EXEMPTIONS)

a. Drug Product Approved Without Official Product Monograph

When a drug product is approved by Health Canada without an official product monograph (i.e., ‘old’ drugs), the ministry will accept information generally included in the official product monograph (listed below) in its place. A manufacturer should submit the following information to satisfy this regulation.

12(2) If Health Canada has not approved a product monograph for a drug product, the manufacturer of the drug product may, instead of submitting a copy of the product monograph as required under clause (1) (a), submit to the executive officer the following information:

1. Pharmaceutical information.
2. Information with respect to the product’s clinical pharmacology.
3. Information as to the product’s indications and clinical use.
4. A list of any contra-indications, warnings or precautions in the use of the product and of possible adverse reactions to its use.
5. A list of symptoms of an overdose of the product and information as to the treatment of an overdose.
6. Information with respect to the dosage and administration of the product.
7. Information regarding the availability of dosage forms for each strength of the product marketed in Canada.

Please refer to the Therapeutic Products Directorate Guidance for Industry: Product Monograph for more detail.

b. Additional Strengths (Brand/Innovator Line Extension Drug Products)

If a submission includes several strengths of a specific dosage form concurrently, or additional strengths of an already-listed drug product, the manufacturer may refer to subsection 12(3) of O. Reg. 201/96 under the ODBA to determine if the exemption for additional strengths applies.

12(3) A manufacturer may satisfy the condition set out in clause (1) (h) for a strength of a drug product by submitting the clinical evidence referred to in clause (1) (h) for another strength of the same dosage form of the drug product, if the evidence is sufficient for the purposes of evaluating the therapeutic effectiveness or efficacy and the safety of both the strengths of the dosage form of the product.

Manufacturers who wish to use this exemption should provide:

- evidence of formulation proportionality (or bioequivalence if not proportional);
- clinical evidence supporting the reference/listed strength(s);
- justification for the additional strength(s); and
- clinical study for the listed strength of the drug product (only the clinical summary data is required).

This exemption allows for the submission of clinical data for one specific strength to be applied to other strengths of the same dosage form of a drug product. If a drug product does not qualify for this exemption, manufacturers must provide separate clinical studies for each strength of the drug product.
Evidence of Proportionality in Composition or 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 proportional formulations (i.e., CPID or 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 in order to rely on the clinical data for another strength of the listed product.

Refer to Health Canada Guidance on formulation proportionality.

Justification for an 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. Although not required with this exemption, it is helpful to have some data for the additional strength of the product in the targeted patient population. The manufacturer should also estimate the proportion of patients in whom the additional strength product would be used.

Although there is an exemption for clinical data for additional strengths of products, there is no exemption for economic data. Manufacturers are still required to describe the economic value and impact of an additional strength as noted in clause 12(1) (i) of the ODBA Regulation.

A manufacturer making a submission for an additional strength of a drug product already listed in the Formulary must still submit copies of the clinical studies for the listed strength of the drug product. The submitted clinical study should be limited to the summary data. Raw clinical or pharmaceutical data (i.e., individual patient level) should not be submitted.
c. **New Formats (Brand/Innovator Line Extension Drug Products)**

If a submission includes a new dosage form, new packaging components and new pack size (new format) of a listed single source product, the manufacturer may refer to subsection 12(3.1) of O. Reg. 201/96 made under the ODBA to determine if the exemption for additional formats applies.

12(3.1) A manufacturer may satisfy the condition set out in clause (1) (h) for a format of a drug product by submitting the clinical evidence referred to in clause (1) (h) for another format of the drug product, if the evidence is sufficient for the purposes of evaluating the therapeutic effectiveness or efficacy and safety of both the formats of the product.

Manufacturers who wish to use this exemption should provide:

- evidence of Health Canada’s approval of the new pack size, new dosage form or new packaging format;

- evidence of bioequivalence/pharmaceutical equivalence between the two formats;

- justification for the new format; and

- clinical studies for the listed format of the drug product (only the clinical summary report).

This exemption allows for clinical data respecting a listed drug product to be applied to new pack sizes, a new dosage form or new packaging formats of a drug product. When a drug does not qualify for this exemption, manufacturers must provide separate clinical studies for each format of the drug product.

This exemption can also be relied upon for submissions that include multiple pack sizes, different dosage forms or different packaging formats of the same drug product.
concurrently. The manufacturer may use the clinical data of a specific strength, dosage form and packaging format to apply to the other formats.

It will be necessary to establish a clear linkage between the reference/ listed format and the other format(s). Although the ministry will be guided by the requirements imposed by Health Canada for the new format, additional clinical evidence or comparative studies may be required to demonstrate that the clinical data for the listed product can be relied upon for the new format. Manufacturers must clearly outline the evidence upon which Health Canada approved the new format.

During the course of their review, the CED may recommend that clinical data are required in order to evaluate whether the new format is suitable for reimbursement. It is likely that, if Health Canada required product specific clinical data before approving the new format, the CED would require the same information. In these instances, manufacturers must provide the clinical evidence. Generally, where a new format is likely to be used in a specific patient population, data in that population is helpful. As well, if the new format is likely to incur additional costs to the program, evidence to justify the additional costs will be required.

**New Pack Size**

For the addition of new pack sizes for a listed drug product, a manufacturer may rely on the same clinical data for the original format of the drug product. The new package size must have the same packaging components in containers and closure systems, etc. Manufacturers must provide the following information:

- Justification of need for the new pack size;
- Confirmation that there is no change in the master formulation;
- Old and new CPIDs or master formulations, as applicable;
- Confirmation that the bioavailability of the product is not affected by the change;
- Evidence of Health Canada’s approval (e.g., NOC or NOL; completed DNF, dated and signed);
- The updated product monograph with the date of revision; and
- A summary report of the clinical trial(s) of the listed product.
New Packaging Format

The ministry requires evidence that Health Canada has considered the efficacy, safety and quality of the new format and has approved it for sale in Canada (e.g., NOC and completed DNF, etc.). Manufacturers must provide the following information:

- Justification of need for the new packaging format;
- Confirmation that there is no change in the master formulation;
- Confirmation that the bioavailability of the product is not affected by the change;
- Evidence of Health Canada’s approval (e.g., NOC or NOL; completed DNF, dated and signed);
- The updated product monograph with the date of revision;
- Evidence of pharmaceutical equivalence (see details below); and
- A summary report of clinical trial(s) of the listed product.

Evidence of Bioequivalence

When the bioavailability of a drug product in a new dosage form or packaging format is not identical to that of the reference/listed 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 another format.

Evidence of Pharmaceutical Equivalence

Manufacturers must submit comparative stability test data for different packaging formats demonstrating that the two formats are equivalent in terms of performance and product quality to support the entire product shelf life.

In addition, a copy of the stability study protocol/design, including the testing frequency, parameters, specifications and methodologies, etc., is required.
**Justification of Need for the New Format**

Manufacturers must provide justification for the new format (dosage form, packaging format or size) and describe the patient population that is most likely to make use of the new format. Although not required with this exemption, it is helpful to have some data with the new format in the targeted patient population. The manufacturer should also estimate the proportion of patients in whom the new format would be used. Although there is an exemption for clinical data for new formats, there is no exemption for economic evidence. Manufacturers are still required to describe the economic value and impact of an additional format as outlined in 12(1) (i) of the ODBA Regulation.

**Clinical Study of the listed Strength/Format of the Drug Product**

A manufacturer making a submission for an additional format of a drug product already listed in the Formulary must still submit copies of the clinical studies for the listed format of the drug product. The ministry will accept a copy of the summary report of the clinical trial of the listed product (i.e., full clinical trial study data is not required). Raw clinical or pharmaceutical data (i.e., individual patient level) should not be submitted.

The tables on the following pages provide guidance as to the data that may be required for new formats.
**Injectable dosage form:** Line extensions may include a new formulation (e.g., dry powder to ready-to-use solution) or a new package format.

<table>
<thead>
<tr>
<th>Line Extension of a Brand Product</th>
<th>Strength</th>
<th>Dosage Form</th>
<th>Route of Administration</th>
<th>Formulation</th>
<th>Package</th>
<th>Required Clinical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New:</strong> Multi-dose pen for injection</td>
<td>Same</td>
<td>Same (injection)</td>
<td>Same (IV)</td>
<td>Different</td>
<td>Different</td>
<td>Clinical data for listed product. Evidence of pharmaceutical equivalence.</td>
</tr>
<tr>
<td><strong>Original:</strong> Single-dose vial for injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>New:</strong> Prefilled Syringe</td>
<td>Same</td>
<td>Same (injection)</td>
<td>Same (IV)</td>
<td>Different</td>
<td>Different</td>
<td>Reference or use of clinical data from listed product. Evidence of pharmaceutical equivalence.</td>
</tr>
<tr>
<td><strong>Original:</strong> Multi-dose vial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>New:</strong> IV Minibag</td>
<td>Same</td>
<td>Same (injection)</td>
<td>Same (IV)</td>
<td>Different</td>
<td>Different</td>
<td>Reference or use of clinical data from listed product. Evidence of pharmaceutical equivalence.</td>
</tr>
<tr>
<td><strong>Original:</strong> Dry powder vial for injection (after reconstitution)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>New:</strong> Multi-dose vial</td>
<td>Same</td>
<td>Same</td>
<td>Same (IV)</td>
<td>Different</td>
<td>Different</td>
<td>Reference or use of clinical data from listed product. Evidence of pharmaceutical equivalence.</td>
</tr>
<tr>
<td>Line Extension of a Brand Product</td>
<td>Strength</td>
<td>Dosage Form</td>
<td>Route of Administration</td>
<td>Formulation</td>
<td>Package</td>
<td>Required Clinical Data</td>
</tr>
<tr>
<td>----------------------------------</td>
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<td>-------------------------</td>
<td>-------------</td>
<td>---------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Original: Dry powder vial for reconstitution</td>
<td>(injection)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>of clinical data from listed product. Evidence of pharmaceutical equivalence.</td>
</tr>
</tbody>
</table>
### Solid oral dosage form: Line extensions may include a new formulation (e.g., tablet versus capsule) or a new dosage form.

<table>
<thead>
<tr>
<th>Line extension of a brand product</th>
<th>Strength</th>
<th>Dosage Form</th>
<th>Route of Administration</th>
<th>Formulation</th>
<th>Package</th>
<th>Required Clinical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New:</strong> tablet</td>
<td>Same</td>
<td>Different</td>
<td>Same (oral)</td>
<td>Different</td>
<td>N/A</td>
<td>Reference or use of clinical data from listed product. Bioequivalence study required.</td>
</tr>
<tr>
<td><strong>Original:</strong> capsule</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>New:</strong> sachet or sprinkle capsules</td>
<td>Same</td>
<td>Different</td>
<td>Same (oral)</td>
<td>Different</td>
<td>Different</td>
<td>Reference or use of clinical data from listed product. Bioequivalence study required.</td>
</tr>
<tr>
<td><strong>Original:</strong> tablet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Oral liquids: Line extensions may include a change in formulation (e.g., oral liquid versus tablet) or a new package format.

<table>
<thead>
<tr>
<th>Line extension of a brand product</th>
<th>Strength</th>
<th>Dosage Form</th>
<th>Route of Administration</th>
<th>Formulation</th>
<th>Package</th>
<th>Required Clinical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New:</strong> oral liquid</td>
<td>Different</td>
<td>Different</td>
<td>Same (oral)</td>
<td>Different</td>
<td>Different</td>
<td>Reference or use of clinical data from listed product. Bioequivalence study required.</td>
</tr>
<tr>
<td><strong>Original:</strong> tablet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Oral liquids, ophthalmic, otic, injectable, inhalation and nasal solutions:** Additional package size to the listed format

<table>
<thead>
<tr>
<th>Line extension of a brand product</th>
<th>Strength</th>
<th>Dosage Form</th>
<th>Route of Administration</th>
<th>Formulation</th>
<th>Package Size</th>
<th>Required Clinical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>New: new size to the existing package format</td>
<td>Same</td>
<td>Same</td>
<td>Same</td>
<td>Same</td>
<td>Different * the new pack size must have the same packaging components and closure system as the listed drug product</td>
<td>Reference or use of clinical data from listed product.</td>
</tr>
<tr>
<td>Original: listed format</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PART III-A.3. AGREEMENTS

a. Disclosure of Information

Subsection 12(7) of the ODBA Regulation provides that if required to do so by the Executive Officer, the manufacturer must enter into a product listing agreement with the Executive Officer that may include a volume discount or other listing requirements and the manufacturer must agree that certain information may be made public as specified below.

12(7) If required by the executive officer, the manufacturer of the product shall enter into an agreement with the executive officer that specifies any volume discount or other amount that may be payable by the manufacturer to the Minister of Finance, and shall agree that the executive officer may make public the following information, and that information only, with respect to the agreement:

1. The name of the manufacturer.
2. The subject-matter of the agreement.
3. The fact of entering into or terminating the agreement.

The manufacturer must agree to the publication of certain information about the agreement: that is, the name of the manufacturer, the subject-matter of the agreement, and the fact of entering into or terminating the agreement. Certain information about the agreement may be reported and published at an aggregate level.

The ministry interprets "subject-matter" to include general topics, such as, "Product Listing Agreement for product x", or "Listing agreements for products x, y, and z", rather than specific details or content of the agreement. Furthermore, the ministry will not share any confidential pricing information or confidential information related to the terms and conditions of the agreements with any third parties, including other provinces or territories.

Please Note: By entering into an agreement with the Executive Officer, the Executive Officer may, in the Executive Officer's sole discretion, state publicly the matters referenced in subsection 12 (7) of the ODBA Regulation, including that the Executive Officer has entered into a pricing agreement.
with the Manufacturer that provides savings to the Ontario Drug Benefit Program. For greater certainty, the Executive Officer will, however, not disclose the pricing amounts as set out in the agreement.

b. Agreements in Force Prior to October 1, 2006

Manufacturers are no longer required to enter into a written agreement that sets out net costs to the Province during subsequent three year periods in relation to the listed drug product or a group of listed drug products that includes the listed drug product. Notwithstanding the foregoing, any agreement that existed before October 1, 2006 will continue to be in force until it expires according to the terms in the agreement.

12.0.1 An agreement that was entered into under this section as it existed before October 1, 2006 continues in force until it expires according to its terms.
To maintain a product listing, the manufacturer must comply with the conditions listed below under the ODBA Regulation:

**CONDITIONS TO CONTINUE TO BE A DESIGNATED LISTED DRUG PRODUCT**

12.1 (1) The following conditions must be met in order for a designated listed drug product to continue to be designated as a listed drug product:

1. The manufacturer of the product shall give the executive officer notice of any change made to the product, including a formulation change, and of any change in the ownership of the manufacturer.

2. The product must be authorized for sale under the *Food and Drugs Act* (Canada).

3. The manufacturer of the product must continue to be able to supply the product at the drug benefit price in a quantity that is sufficient to meet the demand for the product.

4. Where the manufacturer was a party to an agreement to which this paragraph, as it read before October 1, 2006, applied, the manufacturer shall continue to be a party to that agreement until it expires according to its terms.

5. Subject to paragraphs 6.1 to 6.8, if the product has been designated as interchangeable under the *Drug Interchangeability and Dispensing Fee Act* the drug benefit price of the product may not be more than the price that could be proposed to the executive officer under section 11.

6. REVOKED: O. Reg. 220/10, s. 4 (2).

6.1 Paragraph 5 does not apply with respect to a product that was designated as interchangeable with an original product on or before March 31, 2013, where there is evidence satisfactory to the executive officer that,

i. the product is the only drug product of its type that is designated as interchangeable with an original drug product, and has been so designated for at least two years, and

ii. removing the product’s listing would result in significant patient safety or access concerns, or significant increased costs to the Government of Ontario.

6.2 Paragraph 5 does not apply with respect to a product that has been designated as interchangeable with an original product where the
manufacturer of the interchangeable product has submitted evidence satisfactory to the executive officer of substantial raw material cost increases or substantial direct manufacturing cost increases, and the executive officer is satisfied that the criteria established under section 12.2 have been met establishing that it is in the public interest that the interchangeable product be listed at a higher drug benefit price.

6.3 If the circumstances described in subsections 11 (2) and (3.2) existed at the time the drug product was submitted for designation, but the executive officer, or in the case of a province or territory outside Ontario but within Canada, the government or other appropriate authority of the province or territory, has since entered into an agreement with the manufacturer of the relevant original product respecting the payment of a volume discount or other amount by the manufacturer in respect of the original product, then on and from the effective date of that agreement, the drug benefit price of the product may not be more than 75 per cent of that of the original product upon which its drug benefit price is based, as of the date when the product was first proposed for designation as interchangeable.

6.4 If the circumstances described in subsection 11 (2) existed at the time the drug product was submitted for designation, but the drug product ceases to be the only drug product of its type that has been designated as interchangeable with an original drug product in Ontario or another product becomes interchangeable with the original product outside Ontario but within Canada, then on and from the date that the ceasing or becoming interchangeable occurs, the drug benefit price of the product may not be more than 50 per cent of that of the original product upon which its drug benefit price is based, as of, 

i. in the case of a product that ceases to be the only drug product of its type that has been designated as interchangeable with an original drug product in Ontario, the date of the ceasing, or

ii. in the case where another product becomes interchangeable with the original product outside Ontario but within Canada, the date when the product was first proposed for designation as interchangeable.

6.5 If the circumstances described in subsection 11 (4) existed at the time the drug product was submitted for designation, but more than two drug products of its type become designated as interchangeable with an original drug product in Ontario or another product becomes interchangeable with the original product outside Ontario but within Canada, then on and from the relevant date, the drug benefit price of the product may not be more than,

i. 25 per cent of that of the original product upon which its drug benefit
price is based, as of the date when the third drug product of the type became designated as interchangeable or 35 per cent in the case of a product that is not a solid dosage form, in the case where more than two drug products of its type become designated as interchangeable with an original drug product in Ontario, or

ii. 25 per cent of that of the original product upon which its drug benefit price is based, as of the date when the product was first proposed for designation as interchangeable or 35 per cent in the case of a product that is not a solid dosage form, in the case where another product becomes interchangeable with the original product outside Ontario but within Canada.

6.6 Paragraphs 6.3 to 6.5 do not apply where the circumstances described in paragraph 6.2 exist.

6.7 Subject to paragraph 6.2, and for greater certainty, if at any time three or more drug products are designated as interchangeable with an original product under the *Drug Interchangeability and Dispensing Fee Act* or are otherwise available interchangeably with the original product within Canada, then from the time the third product becomes or is designated as interchangeable, none of the price exceptions in this subsection shall apply with respect to any of the drug products listed in Ontario, and the drug benefit price from that time shall be no higher than,

i. 25 per cent of that of the original product, as of the date when the third drug product of the type became designated as interchangeable or 35 per cent in the case of a product that is not a solid dosage form, in the case where three or more drug products are designated as interchangeable with an original product under the *Drug Interchangeability and Dispensing Fee Act*,

ii. 25 per cent of that of the original product, as of the date when the second drug product of the type became designated as interchangeable or 35 per cent in the case of a product that is not a solid dosage form, in the case where two drug products are designated as interchangeable with an original product under the *Drug Interchangeability and Dispensing Fee Act*, and one or more other products become interchangeable with the original product outside of Ontario but within Canada, or

iii. 25 per cent of that of the original product, as of the date when the product was first proposed for designation as interchangeable, or 35 per cent in the case of a product that is not a solid dosage form in the case where the product is the only product of its type designated as interchangeable with the original product under the *Drug
Interchangeability and Dispensing Fee Act, and two or more other products become interchangeable with the original product outside Ontario but within Canada.

6.8 Paragraphs 6.3 to 6.7 apply to a product designated as interchangeable on or after April 1, 2013.

7. If required by the executive officer, the manufacturer of the product shall enter into and remain a party to an agreement with the executive officer that specifies any volume discount or other amount that may be payable by the manufacturer to the Minister of Finance, and shall agree that the executive officer may make public the following information, and that information only, with respect to the agreement:

i. The name of the manufacturer.

ii. The subject-matter of the agreement.

iii. The fact of entering into or terminating the agreement.

8. If required by the executive officer, the manufacturer of a product that has been designated as interchangeable under the Drug Interchangeability and Dispensing Fee Act shall inform the executive officer of the price that the manufacturer receives for the product, net of the value of any ordinary commercial terms. O. Reg. 459/06, s. 9; O. Reg. 559/06, s. 2 (1, 2); O. Reg. 320/07, s. 3 (1-4); O. Reg. 355/08, s. 3 (1-3); O. Reg. 220/10, s. 4 (1-4); O. Reg. 115/15, s. 2 (1-3).

(2) For greater certainty, the conditions set out in subsection (1) apply whether the designation as a listed drug product or as an interchangeable product under the Drug Interchangeability and Dispensing Fee Act took place before, on or after July 1, 2010. O. Reg. 459/06, s. 9; O. Reg. 220/10, s. 4 (5).

(3) Where the circumstances described in paragraph 6.1 or 6.2 of subsection (1) exist, the executive officer may, in the executive officer’s sole discretion, negotiate an agreement with the manufacturer for any drug benefit price, but,

(a) in no case may the interchangeable product be priced higher than the original product, unless,

(i) the manufacturer has submitted detailed information to the executive officer demonstrating why the product should be priced higher than the original product, and

(ii) the executive officer considers such a price to be in the public interest, having regard to the matters set out in subsection 22 (2) of
the Act and to anything else the executive officer considers relevant; and

(b) in respect of a product for which the only applicable circumstances are those set out in paragraph 6.1 of subsection (1), if the circumstance set out in subparagraph 6.1 i of subsection (1) no longer applies, the drug benefit price of the product shall revert to a price that is less than or equal to 25 per cent of the drug benefit price of the original product as set out in the Formulary on the date that the product was first proposed for designation as a listed drug product. O. Reg. 220/10, s. 4 (6).

(4) Despite anything else in this section, if the circumstances described in subsection 11 (2) existed at the time the drug product was submitted for designation and 120 days before the second anniversary of the designation, paragraph 6.4 of subsection (1) does not apply, then the executive officer may, in the executive officer’s sole discretion, review the drug benefit price of the product and agree to continue to list the product at the price at which it was designated or propose a lower drug benefit price. O. Reg. 115/15, s. 2 (4).

(5) If the executive officer commences a review of the drug benefit price of a product under subsection (4), then it is a condition of continuing to be designated as a listed drug product that the manufacturer of the product, within a reasonable time period specified by the executive officer, provide the executive officer with any information that the executive officer considers necessary for reviewing the drug benefit price of the product, including, but without being limited to,

(a) raw material costs;
(b) manufacturing costs;
(c) cost of goods sold;
(d) the price of the product in comparable jurisdictions outside of Canada; and
(e) specialized labour costs or unique market conditions that might result in significant patient safety or access concerns or significant cost increases to the Government of Ontario if the product is not continued to be listed at the same drug benefit price. O. Reg. 115/15, s. 2 (4).

(6) The executive officer shall remove the designation of the product if, following the executive officer’s review of the drug benefit price of the product under subsection (4), the executive officer and the manufacturer cannot agree on a price within 60 days of the executive officer receiving all
of the information mentioned in subsection (5) that the executive officer considers necessary to make the decision. O. Reg. 115/15, s. 2 (4).(7) Subsections (4), (5) and (6) apply to a product designated as interchangeable on or after April 1, 2013. O. Reg. 115/15, s. 2 (4).

(8) For the purposes of this section, in determining the price of an original product as of the applicable date, the executive officer may make the adjustments set out in subsection (9) in determining the price of the original product in the case of an interchangeable product, where,

(a) the original product has not been a listed drug product or has not been sold in Ontario for at least 10 years; and

(b) the interchangeable product is one of no more than two listed drug products that are designated as interchangeable with the original product. O. Reg. 115/15, s. 2 (4).

(9) The adjustments mentioned in subsection (8) are as follows:

1. Determine the highest drug benefit price at which the original product was listed.

2. Commencing in the year in which the original product ceased to be listed or sold in Ontario, add an amount to reflect the average increase in consumer prices shown in Statistics Canada’s Consumer Price Index for Ontario (All Items) for each succeeding year to,
   
i. a maximum of 10 years, or
   
ii. a number of years determined by the executive officer that exceeds 10, where the executive officer is satisfied that it is in the public interest to make such a determination. O. Reg. 115/15, s. 2 (4).

Please refer to the regulations made under the Ontario Drug Benefit Act (ODBA) and the Drug Interchangeability and Dispensing Fee Act (DIDFA) if you are unclear as to submission requirements. In the event of a conflict between these Guidelines and the regulations made under the ODBA or DIDFA, the regulations prevail.

Paragraph 1 of subsection 12.1(1) requires that the manufacturer notify the ministry of Health Canada Level I and II changes to its drug products listed in the Formulary, and allows the ministry to make changes, as appropriate, to the Formulary. Details about Health Canada Level I and II changes are available on their website. The ministry must be notified of any change to the DIN or ownership of the manufacturer, significant changes to the product monograph or master formulation, or changes that affect the bioavailability of the drug product. This is a requirement for
all drug products listed on the Formulary, including those products reviewed through the CDR or pCODR process.

Manufacturers should clearly indicate which products are affected by the change. Manufacturers should not notify the ministry of changes to products that are currently not listed on the Formulary. The ministry will only acknowledge changes received for products listed on the Formulary. The ministry may return the list to manufacturers to identify the affected products before it proceeds in assessing the change.

A separate notification submission is required for each drug affected by Level I or II changes.

Paragraph 2 of subsection 12.1(1) requires that the manufacturer of the product must comply with Health Canada’s requirements, including having a valid NOC and/or DIN and be authorized for sale under the *Food and Drugs Act* (Canada).

In addition to the above, the following conditions must be met in order for a single source drug product to continue to be designated as a listed drug product:

- the manufacturer must be able to continue to supply the product at the drug benefit price in a quantity that is sufficient to meet the demand for the product;

- if the manufacturer was a party to an agreement to which paragraph 4 of subsection 12.1(1) of the ODBA Regulation (as it read before October 1, 2006) applied, the manufacturer shall continue to be a party to that agreement, until the agreement expires according to its terms;

- if the product is designated as interchangeable under the *Drug Interchangeability and Dispensing Fee Act*, the drug benefit price of the product must comply with paragraphs 5 to 6.8 of subsection 12.1(1) of the ODBA Regulation (see section below); and

- if required by the Executive Officer, the manufacturer must enter into an agreement with the Executive Officer and agree to the publication of certain information about the agreement: that is, the name of the manufacturer, the subject-matter of the agreement, and the fact of entering into or terminating the agreement. Please refer to Part III.A.3 for the information that will be disclosed.
**Note:** If the Executive Officer believes on reasonable grounds that a manufacturer is not selling its listed product at the DBP for the purposes of supplying a product under the ODBA, the Executive Officer may make an order under section 11.4 of the ODBA requiring the manufacturer to pay to the Minister of Finance the difference as set out in the ODBA.

**Pricing of Interchangeable (Generic) Drug Products**

In order for an interchangeable product that has been designated as a listed drug product under the ODBA to continue to be designated as a listed drug product, the drug benefit price of the product may not be more than the price that could be proposed to the executive officer under section 11 of the ODBA Regulation (see below and Part III-B.1 of these Guidelines):

- For multi-source generic products in solid dosage forms – 25% of the drug benefit price of the original product
- For multi-source generic products in non-solid dosage forms – 35% of the drug benefit price of the original product
- For dual source generic products – 50% of the drug benefit price of the original product
- For single source generic products where there is a product listing agreement between the ministry and the manufacturer of the original product – 75% of the drug benefit price of the original product
- For single source generic products where there is no product listing agreement between the ministry and the manufacturer of the original product – 85% of the drug benefit price of the original product.

Despite the pricing rules noted above, the Executive Officer may agree to increase the drug benefit price of an interchangeable product in the following circumstances:

1. A single source generic product listed prior to April 1, 2013 that has remained single source for at least two years and requires a price increase to stay on the Formulary. The manufacturer must submit evidence satisfying the Executive Officer that removing the product’s listing would result in significant patient safety or access concerns, or significant increased costs to the Government of Ontario [see paragraph 6.1 of subsection 12.1(1)].

2. A generic product (single-, dual- or multi-source) that requires a price increase due to substantial raw material cost increases or substantial direct manufacturing cost increases.
The manufacturer must submit evidence satisfying Executive Officer of the raw material / direct manufacturing cost increase and that the price increase is in the public interest [see paragraph 6.2 of subsection 12.1(1)].

3. A dual- or multi-source generic product listed on or after April 1, 2013 that moves up a tier due to the discontinuation of a competitor generic (i.e., dual source product becomes single source, and multi-source product becomes dual source). The generic is then priced at the new tier (i.e. 75% or 85% if the product becomes single source, and 50% if the product becomes dual source) [see subsections 12.1(6.3) to (6.5)]. Currently the Saskatchewan Drug Plan notifies the provinces and territories when this happens.
PART III-A.5. NOTIFICATION OF CHANGE TO THE DRUG PRODUCT

Paragraph 1 of subsection 12.1(1) of the ODBA Regulation requires that manufacturers notify the ministry of Health Canada Level I and II changes to its drug products (details about Health Canada Level I and II changes are available on their website. Without limiting the generality of the ODBA Regulation, the ministry must be notified of any change to the DIN or ownership of the manufacturer, significant changes to the product monograph or master formulation, or changes that affect the bioavailability of the drug product.

12.1 (1) The following conditions must be met in order for a designated listed drug product to continue to be designated as a listed drug product:

1. The manufacturer of the product shall give the executive officer notice of any change made to the product, including a formulation change, and of any change in the ownership of the manufacturer.

The ministry requires manufacturers to submit notification of Health Canada Level I and II changes. In addition, manufacturers must also report to the ministry changes in:

- ownership
- DIN
- company name
- drug product name
- product monograph

Manufacturers should clearly indicate which products are affected by the change. Manufacturers should not notify the ministry of changes to products that are currently not listed on the Formulary. The ministry will only acknowledge changes received for products listed on the Formulary. The ministry may return the list to manufacturers to identify the affected products before it proceeds in assessing the change. A separate notification submission is required for each drug.
A manufacturer must report Level I and II changes and the above additional types of change to its listed drug products within 30 days of receipt of approval from Health Canada. A Notice of Change submission must be completed within this timeframe. Each notification of change must be dated and signed by a senior company official.

Please note that this process is new to both Health Canada and the ministry. Therefore, the ministry reserves the right to request additional information or material as deemed appropriate.

Justification/rationale should be provided where certain information is not available, otherwise the submissions will be deemed as incomplete.

Note - when bioavailability has been affected, a new submission, including new comparative bioequivalence/clinical data, is required.

To simplify administrative changes, a maximum of ten drug products of the same drug substance per submission is suggested as a guideline.

For each type of change noted below, the ministry must receive the listed documentation in order for a drug product to continue to be designated as a benefit in the Formulary.

a. **Change in DIN, Ownership, Company Name and Drug Product Name**

- Signed and dated cover letter on company letterhead that includes:
  
  a) The type of notification (i.e., level of change);
  
  b) Narrative of the change(s);
  
  c) A brief rationale for the change(s);
  
  d) Listing of all drug products, including the DIN(s), which are affected by the change(s), and if available, a reference to Drug Submission Master File Number(s) and Product File Number(s);
  
  e) Confirmation that the master formulation has not changed; and
  
  f) Confirmation that the bioavailability has not been affected.

- Evidence that Health Canada has approved the change:
a) Notice of Compliance (NOC) and/or No Objection Letter (NOL);
b) Where No Objection Letter is not available, linkage information such as email correspondence with Health Canada; and
c) Completed, dated and signed Drug Notification Form (DNF) reflecting the old and new changes (as applicable) (e.g., DIN, manufacturer name, company name or drug product name, for each drug product affected).

- Updated product monograph (annotated/tracked and non-annotated) with most recent date of revision and control number.

b. Product Monograph Changes

For changes to the product monograph where bioavailability has been affected, a submission including the new comparative bioequivalence/clinical study is required. Refer to guidelines for the appropriate submission requirements.

Only significant changes to the product monograph must be brought to the attention of the ministry. Significant changes include any changes to indications, contraindications, adverse effects, dosage regimen, and warning/precautions.

- Signed and dated cover letter on company letterhead that includes:
  a) The type of notification (i.e., level of change);
  b) Narrative of the change(s)
  c) A brief rationale for the change(s); and
  d) Listing of all drug products, including the DIN(s), which are affected by the change(s), and if available, a reference to Drug Submission Master File Number(s) and Product File Number(s).

- Evidence that Health Canada has approved the change:
  a) Notice of Compliance (NOC) and/or No Objection Letter (NOL);
  b) Where No Objection Letter is not available, linkage information such as email correspondence with Health Canada; and
c) Updated product monograph (annotated/tracked and non-annotated) with most recent date of revision and control number.

**Note:** For Level III changes where Health Canada has not issued an NOC or No Objection Letter and/or updated product monograph, the following information is required:

i. Confirmation that the product is a Level III notification of change as per Health Canada’s Post NOC Changes Notice.

ii. Evidence showing the product meets Level III criteria and conditions as per Health Canada’s Post NOC Changes Notice (print and submit a copy of the criteria and conditions corresponding to the changes made to the submitted product).

iii. A copy of correspondence (letter or email) between the manufacturer and Health Canada regarding notification of change, if available.

iv. Evidence that the changes have been approved internally by the company. The manufacturer is required to provide an internal approval form of the changes or “change control document”. The approval form must contain the product information-DIN, product name, strength, dosage form, package format, size, nature of change, reference document, implemented by (signed and dated) and approved by (signed and dated).

v. A copy of the annual notification of change, if applicable.
c. Master Formulation Changes

Minor changes in the master formulation (where bioavailability is not affected)

- Signed and dated cover letter on company letterhead that includes:
  
  a) The type of notification (i.e., level of change);
  b) Narrative of the change(s);
  c) A brief rationale for the change(s);
  d) Listing of all drug products, including the DIN(s), which are affected by the change(s), and if available, a reference to Drug Submission Master File Number(s) and Product File Number(s);
  e) Confirmation that the master formulation has changed;
  f) A list of all changes made to the master formulation, including the percent (%) change in the quantity of ingredient(s);
  g) Confirmation that the % change in ingredients does not exceed established limits in Health Canada’s guidance or the policy on Bioequivalence of Proportional Formulation: Oral solid Dosage; and
  h) Confirmation that bioavailability has not been affected.

- Evidence that Health Canada has approved the change:
  
  a) Notice of Compliance (NOC) and/or No Objection Letter (NOL);
  b) Where No Objection Letter is not available, linkage information such as email correspondence with Health Canada; and
  c) Completed Drug Notification Form (DNF), dated and signed.

- Old and new master formulations (CPIIDs) and highlights to the changes reflecting the old and new DINs for the drug product, clearly identifying the strengths and dosage forms affected by the change (if applicable); and

- Updated product monograph (annotated/tracked and non-annotated) with the date of revision and control number; and
• Additional linkage information demonstrating that Health Canada has approved the change (e.g., new cross-licensing agreement).

**Major changes in the master formulation (changes which may affect bioavailability)**

• Signed and dated cover letter on company letterhead that includes:

  a) The type of notification (i.e., level of change);
  b) Narrative of the change(s);
  c) A brief rationale for the change(s);
  d) Listing of all drug products, including the DIN(s), which are affected by the change(s), and if available, a reference to Drug Submission Master File Number(s) and Product File Number(s);
  e) Confirmation that the master formulation has changed and bioavailability is affected; and
  f) A list of all changes made to the master formulation, including the percent (%) change in the quantity of ingredient(s).

• Evidence that Health Canada has approved the change:

  a) Notice of Compliance (NOC) and/or No Objection Letter (NOL);
  b) Where No Objection Letter is not available, linkage information such as email correspondence with Health Canada; and
  c) Completed Drug Notification Form (DNF), dated and signed, reflecting the old and new DINs for the drug product, clearly identifying the strengths and dosage forms affected by the change (if applicable).

• Old and new master formulations (CPIDs);

• Updated product monograph (annotated/tracked and non-annotated) with the date of revision and control number; and

• New comparative bioavailability data.
d. **Changes Not Approved by Health Canada and Other Changes**

If Health Canada has not approved the change (i.e., “old” drugs) post-NOC or -DNF, the manufacturer should submit documentation to support the new changes:

- Signed and dated cover letter on company letterhead that includes:
  a) The type of notification (i.e., level of change, if available);
  b) Narrative of the change(s);
  c) A brief rationale for the change(s);
  d) Listing of all drug products, including the DIN(s), which are affected by the change(s), and if available, a reference to Drug submission Master File Number(s) and Product File Number(s);
  e) Confirmation that the master formulation has/has not changed; and
  f) Confirmation that the bioavailability has/has not been affected.

- Evidence that Health Canada has previously approved the original product:
  a) Original Notice of Compliance (NOC)
  b) Original completed Drug Notification Form (DNF), dated and signed;

- Old and new master formulation with the differences highlighted;

- Updated product monograph (annotated/tracked and non-annotated) with date of revision; and

- Justification why a bioavailability study is not required; or

- Evidence of interchangeability of the old and new formulations (e.g., clinical/bioequivalence study, pharmaceutical equivalence study, etc.), as applicable.
e. Change in Approved Drug Indication(s)

**Note:** A full new submission is required for new indications approved by Health Canada for all products listed as non-General Benefit products in the Formulary.

**Products listed as a General Benefit in the Formulary**

If Health Canada has approved the change, the manufacturer should submit documentation demonstrating that the bioavailability of the drug product was not affected.

- Signed and dated cover letter on company letterhead that includes:
  - a) The type of notification (i.e., level of change);
  - b) Narrative of the change(s);
  - c) A brief rationale for the change(s);
  - d) Listing of all drug products, including the DIN(s), which are affected by the change(s), and if available, a reference to Drug Submission Master File Number(s) and Product File Number(s);
  - e) Confirmation that the master formulation has not changed; and
  - f) Confirmation that bioavailability has not been affected.

- Evidence that Health Canada has approved the change:
  - a) Notice of Compliance (NOC) and/or No Objection Letter (NOL);
  - b) Where No Objection Letter is not available, linkage information such as email correspondence with Health Canada; and
  - c) Completed Drug Notification Form (DNF), dated and signed.

- Updated product monograph (annotated/tracked and non-annotated) with the date of revision and control number;

- Old and new master formulation with the differences highlighted, if applicable; and

- Additional linkage information that Health Canada has approved the change (e.g., new cross-licensing agreement).
Please note: The ministry reserves the right to require a full new submission for any new indication.

f. Changes in the Container Closure System where the Primary Packaging Component is not affected*:

- Signed and dated cover letter on company letterhead that includes:
  a) The type of notification (i.e., level of change);
  b) Narrative of the change(s);
  c) A brief rationale for the change(s);
  d) Listing of all drug products, including the DIN(s), which are affected by the change(s), and if available, a reference to Drug Submission Master File Number(s) and Product File Number(s);
  e) Confirmation that the master formulation has not changed; and
  f) Confirmation that the bioavailability has not been affected.

- Evidence that Health Canada has approved the change:
  a) Notice of Compliance (NOC) and/or No Objection Letter (NOL);
  b) Where No Objection Letter is not available, linkage information such as email correspondence with Health Canada; and
  c) Completed Drug Notification Form (DNF), dated and signed.

- Old and new DNF reflecting the old and new DIN(s) for the drug product, clearly identifying the strengths and dosage forms affected by the change (if applicable);

- Updated product monograph (annotated/tracked and non-annotated) with the date of revision and control number;

- Old and new master formulation/CPID with differences highlighted, if applicable; and

- Additional linkage information that Health Canada has approved the change e.g. new cross-licensing agreement.

*If changes have occurred to the primary packaging component of the drug product, a submission for a new format is required. Please refer to Part III-A.2.
For any type of changes not discussed above, please contact the ministry for guidance about documentation requirements.
PART III-A.6.  MULTIPLE SOURCE (GENERIC) DRUG PRODUCTS FOR SINGLE SOURCE LISTING

Comparative Bioavailability Studies

The manufacturer must provide the following information:

- a completed Clinical Data Checklist; and

- published clinical evidence for the reference product; and

- evidence of bioequivalence with the reference product.

Manufacturers may request listing of a generic product as a single source product under subsection 12(4) of O. Reg. 201/96 made under the ODBA, if another brand/dosage form/strength of the particular drug is not already listed on the Formulary. The primary purpose of subsection 12(4) is to allow a manufacturer to make a submission for a generic product under ODBA when there is no listing of the original/innovator reference drug product.

12(4) A manufacturer may satisfy the condition set out in clause 12(1)(h) for a drug product by submitting to the executive officer the clinical evidence referred to in clause 12(1)(h) with respect to another product and submitting evidence that satisfies the executive officer that the two products are bioequivalent.

12(5) Subsection (4) does not apply if the drug product that the manufacturer seeks to have designated is the drug product of a drug for which there exists a listed drug product.
When this exemption applies, the manufacturer of the multiple source drug product may be exempt from the clinical requirements specified in clause 12(1)(h), but must satisfy all other requirements specified in Section 12 of the ODBA Regulation.

**Clinical Data Checklist and Clinical Evidence**

Manufacturers must provide a completed Clinical Data Checklist, in addition to copies of the published pivotal clinical trials for the reference product. More information on the Clinical Data Checklist and clinical evidence can be found in the interpretation of clause 12(1)(h) of O. Reg. 201/96 made under *ODBA*.

**Published Clinical Evidence for the Reference Product**

When this exemption applies, the manufacturer of the generic drug product(s) may be exempt from the clinical requirements specified in subsection 12. (1)(h) of the ODBA Regulation, but must provide copies of the published pivotal clinical trials for the reference product.

In addition, the submission must satisfy all other requirements specified in Section 12 of the ODBA Regulation.

**Evidence of Bioequivalence**

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 and Pharmacokinetic/Statistical Worksheet, and the master formulation of the biolot.
PART III-A.7. CLARIFICATION REGARDING EXCEPTION UNDER SUBSECTION 12(6)

12(6) Subsection (1) does not apply to a drug product that is designated as an interchangeable product under the *Drug Interchangeability and Dispensing Fee Act*.

ALL single source and multiple source drug product submissions are guided by the ODBA and the DIDFA. The drug products requested for listing in the Formulary must satisfy the requirements under section 6 of Reg 935 under the Drug Interchangeability and Dispensing Fee Act (DIDFA) or under section 12 of O. Reg. 201/96 under the Ontario Drug Benefit Act (ODBA).
PART III-B

SUBMISSION REQUIREMENTS FOR MULTIPLE SOURCE DRUG PRODUCTS
(GENERIC DRUG PRODUCTS)

DRUG INTERCHANGEABILITY AND DISPENSING FEE ACT (DIDFA)

REG. 935, SECTION 6
REG 201/96, SECTION 11
Multiple Source Drug Products

A manufacturer submitting a multiple source drug product (i.e., new or change in cross-referenced to a listed drug products e.g. new business arrangement) for interchangeability and/or funding consideration should refer to this section for the interpretation of sections 6 to 8 of the DIDFA Regulation and section 11 of the ODBA Regulation.

A submission for an interchangeable product must meet the regulatory requirements as prescribed in the DIDFA Regulation, section 11 of the ODBA and the policy requirements as set out below. A submission must include all applicable supporting documentation in order to be deemed complete.

The ministry has harmonized its review of the majority of generic drugs considered under the DIDFA with that of Health Canada. Solid oral dosage forms for systemic effect, dermatological products that contain one or more glucocorticoids as the only active ingredient(s), transdermal products for systemic effect designated by Health Canada as equivalent to an original/innovator product, and certain aqueous solutions designated by Health Canada as equivalent to an original/innovator product on/after February 15, 2005, undergo a “streamlined” submission and review process.

In general, streamlined submissions will not be reviewed by the CED. All other (i.e., non-streamlined) submissions will continue to be reviewed by the CED.

For detailed information on the screening process and the scheduled new submission deadline applicable to streamlined and non-streamlined submissions, refer to Part II.

If a submission is incomplete, the manufacturer must wait until the following monthly new submission deadline before its drug product submission will be screened.

Please be aware that the onus is on the manufacturer to provide the ministry with complete and accurate information regarding its submission.
For non-streamlined submissions, once the full CED review process is completed by the indicated deadlines, including the ratification of the minutes from the CED meeting and product negotiations with the ministry, the submission review process will be considered complete. All recommendations will be submitted to the EO and are subject to the EO’s review and decisions for inclusion in the next monthly Formulary update.

**Please Note:** The ministry’s review of multi-source product submissions is comprised of two stages: (1) NDSS and (2) CED recommendation. The date of the complete NDSS letter determines the ranking of the product versus another in the CED review process. The date on the CED recommendation letter sent to the manufacturers refers to that the CED review process is complete.
PART III-B.1. ORIGINAL/ INNOVATOR PRODUCT CURRENTLY LISTED AS A BENEFIT

a. Submission Summary Sheet DIDFA

Every submission must include a copy of the completed Submission Summary Sheet. A template has been developed to assist manufacturers in providing all relevant submission requirements. In addition, various template letters, worksheets, tables and other summaries have been developed to ensure all relevant information is provided.

These templates, letters, worksheets, tables and other summaries are provided for the assistance and information of manufacturers only. *In the event that any conflict or discrepancy between these documents and the regulations under the ODBA and the DIDFA, the regulations prevail.*

Templates are located in Part VII of the Guidelines, or refer to ministry’s website for up-to-date copies of these documents.


If a template is altered, the ministry reserves the right to deem the submission incomplete.

b. Cover Letter

The manufacturer must provide a cover letter for each submission and ensure the following is included:

- The brand name, generic name, strength, dosage form (including the various package sizes, as applicable) to be considered for reimbursement consideration

- The cover letter should include a subject heading that adheres to the following format:
Re: <insert product name/generic name, strength, dosage form, package format and size > (the “Product”) manufactured by <insert name of manufacturer> (“the Manufacturer”); and ministry assigned Master File No. and Product File No, if applicable

- Indicate if there are any business agreements or arrangements with any third party (e.g., consultant, cross-licensed, co-marketing, etc.) if applicable

- If there is third party involvement, indicate whether the third party has filed information with Health Canada

- The regulation under which the submission is being made (e.g. Reg 935)

- Identify the type of submission proposed for review (i.e. new multiple source drug product, additional strength, additional dosage form, OFI drug product, etc)

- The program under which listing is proposed (e.g., ODB, NDFP, EAP, etc.)

- Any applicable regulatory exemptions being sought

- Provide the name of the reference product for interchangeability assessment

- For interchangeable products where Health Canada has made a declaration of equivalence (DoE) on the Notice of Compliance (NOC), indicate whether the reference product is a Canadian or Non Canadian Reference Product (NCRP), and provide justification for the use of a NCRP for submissions

- Where the product name or the name of the manufacturer of the reference product is different from the original/innovator Canadian Reference Product, provide evidence to demonstrate the linkage between the different reference products
c. Evidence of Approval from Health Canada

6(1)(a) It is a condition for each strength and dosage form of a drug product to be designated as interchangeable with other products that the manufacturer of the drug product submit to the executive officer, evidence that Health Canada has approved the product for sale in Canada, a copy of the product’s drug notification form issued by Health Canada and, subject to subsection (2), a copy of the product monograph approved by Health Canada;

The ministry requires evidence that Health Canada has considered the efficacy, safety and quality of a drug product and has approved it for sale in Canada. The following documents will be accepted as evidence of approval by Health Canada:

- Notice of Compliance (NOC); and
- Completed Drug Notification Form (DNF) dated and signed; and
- Product Monograph approved by Health Canada.

Notice of Compliance and Drug Notification Form

The ministry requires a copy of the original and the most recent NOC approved by Health Canada for sale of its product and the most recent Product Monograph with matching control number and the date of revision.

If a drug product is approved without a NOC (i.e., “old” drugs), only the DNF is required. The DNF must be completed, dated and signed by a senior company official. Post-dated DNFs will not be accepted as complete.

A Notice of Compliance with Conditions (NOC/c) is accepted and considered as a NOC by the ministry. However, the manufacturer must submit a copy of the updated NOC to the ministry when approved by Health Canada to complete file information.
Product Monograph

A manufacturer must submit the most recently approved Health Canada Product Monograph (if different from the product monograph), with company name, with control number, approval date, the date of revision (if applicable), and tracked changes (as well as evidence that Health Canada has approved the changes [i.e., No Objection Letter (NOL), Notice Of Compliance (NOC) etc.]).

Possible Exemptions

If Health Canada did not approve a product monograph (e.g., “old” drugs), the manufacturer should submit the information generally included in the product monograph, as described in subsection 6(2) of Reg. 935 under the DIDFA. Refer to the Therapeutic Products Directorate’s Common Technical Document: Product Monograph for further detail.

d. Third Party Involvement (e.g. cross-licensed, cross-referenced, consultant on behalf of NOC holder submissions)

The manufacturer named on the Notice of Compliance (NOC) or Drug Notification Form (DNF) who is responsible for the product in Canada may file a submission with the ministry. It is possible that a party other than the manufacturer named on the NOC or DNF may file a submission. It is also possible that a third party may be involved with a submission in other ways (e.g., product fabrication, or product marketing). Where the third party assumes the right to distribute and sell a drug, they will be considered to assume responsibility for the product and certain confirmations will be necessary from the third party. Where the third party acts as an agent only, on behalf the NOC holder, all of the confirmatory documentation will be required from the NOC holder.

Under these circumstances, additional documentation will be necessary to clearly establish the relationship of the third party with the holder of the NOC. The submission will not be deemed complete unless sufficient documentation of all aspects of the submission and the relationships between all parties and drug products are provided and well understood. The Formulary/CDI will list the name of the manufacturer holding the NOC.

When a third party is involved in a submission, the following documentation must be provided:
- **Third Party Authorization/Business Agreement** - Where a third party is involved with a submission, a letter should be submitted from both the NOC holder and the third party confirming the business arrangement between the submitting party and the NOC holder. Manufacturers must also identify if the third party has information on file with Health Canada on New Drug Submission or Abbreviated New Drug Submissions for Subsequent Market-Entry (NDS/ANDS). Depending on the nature of the relationship, the letter from the NOC holder must provide an authorization to the third party to assume responsibility for the submission or authorization to submit the product on the NOC holder's behalf.

- **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. Supplemental NOC should be submitted as necessary.

- **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.

- **Product Confirmation Letter** - A letter from both the NOC holder and the third party who has information filed with Health Canada, dated and signed by a senior company official confirming that the submitted drug product is identical in chemistry and manufacturing, except for labelling and embossing/markings, to the drug product approved on the NOC. Refer to template letter in Part VII of the Guidelines.

- **Proposed Drug Benefit Price** - The NOC holder or the third party that holds the rights to sell the submitted product in Canada must provide the proposed Drug Benefit Price in accordance with section 6(1)(d) of Reg. 935. Refer to template letter in Part VII of the Guidelines.

- **Confirmation of Provided No Rebate Letter** - The manufacturer must certify in writing that no rebates were provided to persons listed under subsection 12.1(1) of the DIDFA with respect to the drug product from the time that Health Canada approved the product for sale in Canada. Refer to template letter in Part VII of the Guidelines.
- **Ability to Supply** - The NOC holder or the third party that holds the rights to sell the submitted product in Canada must also provide the confirmation of ability to supply the product at the proposed drug benefit price in a quantity sufficient to meet the anticipated demand for the product, in accordance with section 6 (1)(e) of Reg. 935. Refer to template letter in Part VII of the Guidelines.


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 proposed drug product submission. The ministry is not looking to enforce patent matters but rather to be made aware of any potential patent infringement prior to listing on the Formulary. The purpose of this requirement is for drug manufacturers to inform the Executive Officer of any limitations in their NOCs. The ministry has, in the past, limited a listing of a drug based on patent restrictions noted in the NOC.

- **Certification Confirming Product is Not a Private Label Product**
  The NOC holder must provide a letter certifying that the submitted drug product is not a private label product. Refer to template letter in Part VII of the Guidelines.
e. Unrestricted Letter of Consent

As federal and provincial governments work to harmonize their drug review processes, it is important for the ministry to be able to communicate freely with other regulatory and review agencies.

6(1)(b) It is a condition for each strength and dosage form of a drug product to be designated as interchangeable with other products that the manufacturer of the drug product submit to the executive officer, a letter authorizing the executive officer to gain access to all information with respect to the product in the possession of Health Canada, the Patented Medicine Prices Review Board established under section 91 of the Patent Act (Canada), 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 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;

Letters should be:

- from the holder of the NOC;
- dated and signed by a senior company official; and
- free of any restrictive clause(s).

Manufacturers must satisfy this requirement by providing a letter of consent which authorizes the ministry to exchange drug product information with the agencies listed in clause 6(1) (b) of the DIDFA Regulation.

The ministry will require an unrestricted letter authorizing it and its agent/designate to access, discuss, use, collect from, and disclose to its agents, consultants, Health Canada, the Canadian Agency for Drugs and Technologies in Health (CADTH) and all persons, parties or entities involved in the CDR procedure, the Patented Medicine Price Review Board (PMPRB), Cancer Care Ontario (CCO) and the government of any province or territory in Canada, all submission information and information in the possession of Health Canada, CADTH, PMPRB, CCO and the government of any province or territory in Canada.
Only letters **free of any restriction** will be accepted. The letter should authorize the ministry to access any information pertaining to the drug product at any time. Manufacturers must not include restrictions or limitations, such as requiring the notification of the manufacturer before obtaining information from Health Canada, having a representative of the manufacturer present when the ministry obtains information, and/or restricting access to a particular Health Canada submission number. A letter with any restrictions will not satisfy this requirement, and the submission will be deemed incomplete.

Please note in the event that a manufacturer delays or does not authorize Health Canada to release submission information when requested by the ministry with this consent letter, the submission will not be moved forward in the review process and the submission may subsequently be deemed incomplete without notification to the manufacturer.

If a manufacturer is applying for the exemption under subsection 6(3), (i.e., pseudogeneric products) the consent letter submitted under clause 6(1) (b) must be submitted by **both** the manufacturer making the submission, and the manufacturer of the original/innovator product. The ministry requires this authorization to be able to access information on file at Health Canada, including the files of the original/innovator product.

When a third party is involved in filing a submission, a letter is required from **all** of the parties which may have information regarding the product on file with Health Canada (e.g. NOC holder, manufacturer, distributor, etc.). If a third party is involved but does not have information on file with Health Canada, please indicate this in the submission.

To assist manufacturers, the ministry has developed template letters which are available in Part VII of the Guideline, and on the ministry’s website. Manufacturers should ensure that required letters are printed on company letterhead and are dated and signed by an appropriate senior company official.


**f. Product Confirmation Letter**

For cross-licensed products, a product confirmation letter from the NOC holder and the other licensee are required. The following format should be followed:
Subject: NOC holder <insert: brand name/ generic name, strength, dosage> (“the Product”) manufactured by NOC holder (“the Manufacturer”) and signed by NOC holder.

Subject: NOC holder <insert: brand name/ generic name, strength, dosage> (“the Product”) manufactured by Other Party (“the Manufacturer”) and signed by Other Party.

To assist manufacturers, the ministry has developed a template letter which is included in Part VII of the Guidelines and on the ministry’s website at:


All letters must be prepared using the appropriate manufacturer’s letterhead, dated and signed by the senior company official.

g. Certified Product Identification Document (CPID) or Master Formula

The NOC for a generic drug product may contain approval for multiple strengths although the bioequivalence study with the original/innovator product may have been done on only one of the strengths. In cases where there is declaration of equivalence (DoE) to the original/innovator product on the NOC and there are multiple strengths of the generic drug product within that NOC, then a Certified Product Information Document (CPID) must accompany the submission to provide evidence of formulation proportionality among the various strengths.

6(1)(c) It is a condition for each strength and dosage form of a drug product to be designated as interchangeable with other products that the manufacturer of the drug product submit to the executive officer, documentation disclosing the product’s master formulation;

The ministry will accept the following:

- completed Certified Product Information Document (CPID) that was approved by Health Canada; or, if unavailable,
- production master formulation (calculated per smallest unit).
A manufacturer must submit the CPID in order to satisfy the exemption for the bioequivalence study requirement as prescribed under subsection 6(4) of the DIDFA Regulation. 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 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.

Please also note if the formulations are not proportional, the comparative bioavailability studies for the other strengths will be required, and the submission will be deemed incomplete.

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 master formulation.

For more information on the CPID, please refer to the Therapeutic Products Directorate’s Quality Overall Summary - Chemical Entities (QOS-CE): as well as Certified Product Information Document - Chemical Entities (CPID-CE).

Reference to another submission file that was sent to the ministry is not acceptable.

Please Note: The ministry reserves the right to ask manufacturers for additional information regarding the master formulation.

Possible Exemptions

Certain types of exemptions may be applicable depending on the drug submission type. Refer to the interpretation under each exemption for the specific criteria:

- This requirement does not apply to “pseudogeneric” drugs for all strengths, as described in subsection 6(3) of the DIDFA Regulations.

- This requirement does not apply to a solid oral dosage form that has been designated by Health Canada as equivalent to the original product or to another listed interchangeable product with which it would be designated as interchangeable (see subsection 6(6) of DIDFA Regulation). However when multiple strengths of these products are submitted, CPID or master formulation will be required as evidence of proportionality for multiple strengths under subsection 6(4).
All submissions for aqueous solutions designated by Health Canada as equivalent (on/after February 15, 2005) to the listed original/innovator product or to another product with which it would be designated as interchangeable are not exempt from this requirement.

h. Proposed Drug Benefit Price

The manufacturer must submit a proposed drug benefit price (DBP) in accordance with section 11 of the ODBA Regulation and sections 6 and 7 of the DIDFA Regulation to be considered for listing on the Ontario Drug Benefit Formulary.

DIDFA Regulation

6. (1) It is a condition for each strength and dosage form of a drug product to be designated as interchangeable with other products that the manufacturer of the drug product submit to the executive officer,

[...

(d) the proposed drug benefit price of the product, where it is proposed that the product be designated as a listed drug product under the Ontario Drug Benefit Act, and a proposed manufacturer’s list price where it is not proposed that the product be so designated;

7. Where it is proposed that the strength and dosage form of a product be designated as interchangeable and it is proposed that it also be designated as a listed drug product under the Ontario Drug Benefit Act, an additional condition to be met in order for it to be designated as interchangeable is that the proposed drug benefit price must be no greater than the price permitted under that Act for the strength and dosage form of the product.

The proposed drug benefit drug price (DBP) should include, where applicable

- the price per smallest unit (e.g. tablet, capsule, gram or milliliter, etc); and
- the price per smallest dispensable unit (e.g., kit, ampoule, pre-filled syringe, vial combination package, etc.); and
- all submitted prices and the DBP must be expressed to four decimal places ($0.0000; $00.0000).

When the manufacturer is seeking interchangeability for more than one package size (e.g., 10mL and 30mL vial), the submission should include the proposed DBP for each package size.

Where more than one DBP is proposed, the lowest price will be used as the DBP, even if the higher price has met the pricing requirement.

Subject to certain exemptions, the regulations made under the ODBA and the DIDFA set the prices of interchangeable generic products at no more than 25 per cent of the original/innovator product price ("25% pricing rule"). These requirements are set out in section 11 of the ODBA Regulation.

Note as well that, subject to certain exemptions, the 25 per cent price rule noted above applies to currently listed products as well as new additions to the Formulary.

**ODBA Regulation**

11. (1) A strength and dosage form of a product that has been submitted for designation as an interchangeable product under the *Drug Interchangeability and Dispensing Fee Act* shall not be designated as a listed drug product unless the manufacturer submits the information required under section 6 of Regulation 935 of the Revised Regulations of Ontario, 1990 (General) made under that Act and the following conditions are met:

1. If the original product is a listed drug product, the drug benefit price of the product proposed to the executive officer under clause 6 (1) (d) of Regulation 935 of the Revised Regulations of Ontario, 1990 must be,
   
   i. less than or equal to 25 per cent of the drug benefit price of the original product as set out in the Formulary,

   A. on the date the product is first proposed for designation as a listed drug product, if no more than two products have already been
designated as interchangeable with the original product, or

B. on the date when the third product became designated as interchangeable with the original product, if three or more products have already been designated as interchangeable with the original product, or

ii. if the drug benefit price of the original product has been reduced by more than 20 per cent in the 24-month period before the date on which the product is proposed for designation as a listed drug product, less than or equal to 25 per cent of the drug benefit price of the original product as set out in the Formulary immediately before the drug benefit price of the original product was first reduced.

2. If the original product was but is no longer a listed drug product, the drug benefit price of the product proposed to the executive officer under clause 6 (1) (d) of Regulation 935 of the Revised Regulations of Ontario, 1990 must be less than or equal to 25 per cent of the highest drug benefit price of the original product that was set out in the Formulary before its removal.

3. REVOKED: O. Reg. 220/10, s. 2 (3).

4. In addition to the applicable conditions under paragraphs 1 and 2, if applicable, and if required by the executive officer, the manufacturer of the product shall enter into an agreement with the executive officer that specifies any volume discount or other amount that may be payable by the manufacturer to the Minister of Finance, and shall agree that the executive officer may make public the following information, and that information only, with respect to the agreement:

   i. The name of the manufacturer.

   ii. The subject-matter of the agreement.

   iii. The fact of entering into or terminating the agreement. O. Reg. 459/06, s. 6; O. Reg. 559/06, s. 1 (1); O. Reg. 355/08, s. 1 (1); O. Reg. 356/08, s. 2; O. Reg. 220/10, s. 2 (1-4); O. Reg. 115/15, s. 1 (1-4).

(1.1) For the purposes of paragraphs 1 and 2 of subsection (1), all references to “25 per cent” shall be read as “35 per cent” in the case of a drug product that is not a solid dosage form. O. Reg. 220/10, s. 2 (5).
(2) Paragraphs 1 and 2 of subsection (1) do not apply where there is evidence satisfactory to the executive officer that the product would be the only drug product of its type that has been proposed to be designated as interchangeable with an original drug product. O. Reg. 559/06, s. 1 (2); O. Reg. 220/10, s. 2 (6).

(3) Where the circumstances described in subsection (2) exist, but subject to subsections (3.1), (3.2) and (3.3), the drug benefit price of the product proposed to the executive officer must be,

(a) less than or equal to 75 per cent of the drug benefit price of the original product as set out in the Formulary on the date the product is first proposed for designation as a listed drug product;

(b) if the drug benefit price of the original product has been reduced by more than 20 per cent in the 24-month period before the date on which the product is proposed for designation as a listed drug product, less than or equal to 75 per cent of the drug benefit price of the original product as set out in the Formulary immediately before the drug benefit price of the original product was first reduced; or

(c) if the original product was but is no longer a listed drug product, less than or equal to 75 per cent of the highest drug benefit price of the original product that was set out in the Formulary before its removal. O. Reg. 115/15, s. 1 (5).

(3.1) Where the circumstances described in subsection (2) exist and there is evidence satisfactory to the executive officer that there is another product listed, sold or available for sale that is interchangeable with the original product outside Ontario but within Canada, the references to “75 per cent” in subsection (3) shall be read as “50 per cent”. O. Reg. 115/15, s. 1 (5).

(3.2) The references to “75 per cent” in subsection (3) shall be read as “85 percent” where the circumstances described in subsection (2) exist and no agreement exists respecting the payment of a volume discount or other amount by the manufacturer in respect of the original product either,

(a) between the executive officer and the manufacturer of the relevant original product; or

(b) between the government or other appropriate authority in any province or territory outside Ontario but within Canada and the manufacturer of the
(3.3) The exceptions set out in subsections (2), (3), (3.1) and (3.2) do not apply where there is evidence satisfactory to the executive officer that there are two or more other products listed, sold or available for sale that are interchangeable with the original product outside Ontario but within Canada, in addition to the product proposed to be designated as interchangeable with the original product in Ontario and, for greater certainty, in those circumstances, the provisions of paragraphs 1 and 2 of subsection (1) apply. O. Reg. 115/15, s. 1 (5).

(4) Paragraphs 1 and 2 of subsection (1) do not apply where, after designation of the proposed product, there would be only two drug products designated as interchangeable with an original drug product. O. Reg. 115/15, s. 1 (5).

(4.1) Where the circumstances described in subsection (4) exist, but subject to subsection (4.2), the drug benefit price of a product proposed to the executive officer must be,

(a) less than or equal to 50 per cent of the drug benefit price of the original product as set out in the Formulary on the date the product is first proposed for designation as a listed drug product;

(b) if the drug benefit price of the original product has been reduced by more than 20 per cent in the 24-month period before the date on which the product is proposed for designation as a listed drug product, less than or equal to 50 per cent of the drug benefit price of the original product as set out in the Formulary immediately before the drug benefit price of the original product was first reduced; or

(c) if the original product was but is no longer a listed drug product, less than or equal to 50 per cent of the highest drug benefit price of the original product that was set out in the Formulary before its removal. O. Reg. 115/15, s. 1 (5).

(4.2) The exceptions set out in subsections (4) and (4.1) do not apply where there is evidence satisfactory to the executive officer that there is another product listed, sold or available for sale that is interchangeable with the original product outside Ontario but within Canada, in addition to the two that are or are proposed to be designated as interchangeable with the original product.
in Ontario and, for greater certainty, in those circumstances, the provisions of paragraphs 1 and 2 of subsection (1) apply. O. Reg. 115/15, s. 1 (5).

(4.3) For greater certainty, nothing in this section shall be interpreted as limiting the authority of the executive officer to maintain an agreement described in subsection 12 (7) or paragraph 7 of subsection 12.1 (1) with the manufacturer of an original product. O. Reg. 115/15, s. 1 (5).

(5) Upon the application of the manufacturer, the executive officer may redesignate a drug product that was designated on the Formulary before December 31, 2007, and whose designation was removed by either of the amendments to the Formulary known as Update 8 to Edition 40, effective January 15, 2008, or Update 8A to Edition 40, effective January 17, 2008, subject to the following:

1. The submission requirements set out in subsection 12 (1) shall be deemed to have been met with respect to the product.
2. The conditions for continued listing set out in section 12.1 must be met with respect to the product.
3. The criteria established by the executive officer under section 12.2 must be met with respect to the product. O. Reg. 355/08, s. 1 (2).

(6) REVOKED: O. Reg. 220/10, s. 2 (8).

(7) Despite paragraphs 1 and 2 of subsection (1), during the three-month period provided for in paragraph 4 of subsection (8), the drug benefit price of a product that meets the conditions set out in subsection (8) must be less than or equal to 50 per cent of the drug benefit price of the original product on the date the product is first proposed for designation as a listed drug product. O. Reg. 220/10, s. 2 (9).

(8) The conditions referred to in subsection (7) are the following:

1. The product is first proposed for designation as a listed drug product on or after April 1, 2012 and has not been designated as a listed drug product at any other time.
2. The manufacturer of the product has submitted evidence satisfactory to
the executive officer that the manufacturer, or another manufacturer of a product that is interchangeable with the original product, has successfully challenged the patent of the original product with the result that the manufacturer’s product can be sold in Canada earlier than if the patent had expired or if the challenge had not been brought.

3. The manufacturer has not entered into any arrangement, other than a cross-licensing agreement, with the manufacturer of the original product with respect to the product that is proposed for designation as a listed drug product, including any first-to-market arrangement or delayed-entry arrangement.

4. The manufacturer agrees that the exception set out in subsection (7) no longer applies three months after the first product of any manufacturer that is interchangeable with the original product becomes a listed drug product, at which time the drug benefit price shall be as set out in subsection (1) or any other applicable provision of this Regulation. O. Reg. 220/10, s. 2 (9).

The original/innovator product price is determined in accordance with the rules set out in paragraphs 1 and 2 of subsection 11(1) of the ODBA Regulation.

In reviewing the proposed price for an interchangeable product the EO may consider, without limiting the generality of the foregoing, both the proposed brand and generic prices, the status of other generic submissions, and any other factor that may be advisable in the public interest.

Interchangeable drug products must be priced at a maximum of 25 percent of the drug benefit price of the listed original/innovator product (the “25% pricing rule”), unless the product is a non-solid dosage form, in which case manufacturers may price a product up to a maximum of 35 percent. There are certain exceptions to this general rule, depending on whether the generic product is the first or second of its kind (see section below).

The drug benefit price of the original/innovator product is:
the price set out in the Formulary on the date the interchangeable drug product is first proposed for designation on the Formulary, in the case of the first, second and third interchangeable products; and

the price set out in the Formulary on the date the third product became designated as interchangeable with the original/innovator product, in the case of the fourth, fifth, sixth or subsequent interchangeable products.

If the original/innovator product is no longer listed i.e., removed from the Formulary or designated as “Not a Benefit”, then the drug benefit price of the original/innovator product is the highest price that was published in the Formulary before the original/innovator product was removed as a benefit.

In cases where the original/innovator product has reduced its price by more than 20% in the last 24 months before the date on which the generic manufacturer has submitted a product for listing, the drug benefit price of the original/innovator product shall be the price set out in the Formulary immediately before the price reduction.

Exemptions:

Certain exemptions may apply to the regulated price rules:

**First or Single Sole Generic Product**

- A single source generic product may apply for a price exemption under subsection 11(2) of the ODBA Regulation. In the request for the price exemption, the manufacturer must demonstrate that its product is the only generic drug product of its type in the Canadian market that is interchangeable with the original/innovator product.

- If the EO is satisfied that the manufacturer’s product is the only generic product of its type, then the product is listed at:
  - 75% of the drug benefit price of the original/innovator product, if there is a product listing agreement between the ministry and the manufacturer of the original/innovator product; or
o 85% of the drug benefit price of the original/innovator product, if there is no product listing agreement between the ministry and the manufacturer of the original/innovator product.

**Second or Dual Source Generic Product**

- A dual source generic product may apply for a price exemption under subsection 11(4) of the ODBA Regulation. In the request for the price exemption, the manufacturer must demonstrate that its product is one of only two drug products in the Canadian market that are interchangeable with the original/innovator product.

- If the EO is satisfied that the manufacturer’s product is dual source, then the product is listed at 50% of the drug benefit price of the original/innovator product, if there is a product listing agreement between the ministry and the manufacturer of the original/innovator product.

Note that the Executive Officer may require the manufacturer of an interchangeable product to enter into a product listing agreement as a condition of being listed on the Formulary, pursuant to paragraph 4 of subsection 11(1) of the ODBA Regulation.

**Price Exemption for Successful Patent Challenge**

- Effective April 1, 2012, generic manufacturers that successfully challenge a patent of the reference brand product may be listed with a drug benefit price of no more than 50% of the original/innovator product price for a period of three months. This period begins when the first generic product is listed on the Formulary. The manufacturer must meet the following condition:

  o The product has not been designated as a listed drug product at any other time.
  o The manufacturer of the product has submitted evidence satisfactory to the executive officer that the manufacturer, or another manufacturer of a product that is interchangeable with the original/innovator product, has successfully challenged the patent of the original/innovator product with the result that the manufacturer’s product can be sold in Canada earlier than if the patent had expired or if the challenge had not been brought.
  o The manufacturer has not entered into any arrangement, other than a cross-licensing agreement, with the manufacturer of the original/innovator product with respect to the product that is proposed for designation as a listed drug product, including any first-to-market arrangement or delayed-entry arrangement.
The manufacturer agrees and accepts that the 50% price exception will cease to apply three months (90 calendar days*) after the first product of any manufacturer that is interchangeable with the original/innovator product becomes a listed drug product, at which time the drug benefit price of the product shall revert to a price that is less than or equal to 25 per cent (or 35 per cent in the case of a drug product that is not a solid dosage form) of the drug benefit price of the original/innovator product as set out in the Formulary on the date that the product was first proposed for designation as a listed drug product.

*Note: In cases where the 90th day does not fall on the effective date of an update to the Formulary, the exception will be deemed to no longer apply on the effective date of the Formulary update that immediately follows the end of the 90 days.

Refer to Part III-B.4. for the information required and the template letter.

DIDFA

- A product will not be designated as a benefit and interchangeable product unless the proposed drug benefit price is equal to or less than the price permitted under the ODBA.
- If the product is a listed drug product under the ODBA, but the manufacturer is not selling the product for the purpose of supplying it to an eligible person under that Act, the manufacturer must not sell the product at a price higher than the drug benefit price permitted under the ODBA.

NDFP Submissions

If the product is requested for NDFP listing, a copy of the following must also be provided:

- All submitted prices must be expressed to four decimal places ($0.0000; $00.0000)
- The proposed reimbursement price should include; where applicable
  1. the price per smallest unit (e.g. tablet, capsule, gram or millilitre, etc); and
  2. the price per smallest dispensable unit for each package size (e.g., bottle, kit, ampoule, pre-filled syringe, vial combination package, etc.); and
  3. the price stated as cost/mg
Final confirmation of pricing arrangements and forecast requirements will be made between CCO and the manufacturer at the time of listing on the NDFP Formulary.

i. Evidence Confirming Ability to Supply

Where it is proposed that the product be designated as a listed drug product in the Formulary, the manufacturer must be able to supply the drug product at the submitted price in a quantity sufficient to meet the anticipated demand in Ontario.

6(1)(e) It is a condition for each strength and dosage form of a drug product to be designated as interchangeable with other products that the manufacturer of the drug product submit to the executive officer, evidence that the manufacturer is able to supply the product at the proposed drug benefit price in a quantity sufficient to meet the anticipated demand for the product where it is proposed that the product be designated as a listed drug product under the Ontario Drug Benefit Act;

In order to satisfy this requirement, the manufacturer must submit a confirmation letter without any restrictions or limitations. The template letter should include a subject heading that adheres to the following format:

[Product name/generic name, strength, and dosage form > (the “Product”) manufactured by <insert name of manufacturer> (“the Manufacturer”).]

To assist manufacturers, the ministry has developed a template letter which is included in Part VII of the Guidelines and on the ministry’s website at:


All letters must be prepared using the appropriate manufacturer’s letterhead, dated and signed by the senior company official.

Please note that the ministry may request additional documentation to satisfy itself that the manufacturer is able to supply the product at the proposed DBP in a quantity sufficient to meet the
anticipated demand for the product where it is proposed that the product be designated as a listed drug product on the Formulary.

**Note**: It is a condition for an approved drug product to be able to meet the anticipated demand at the time of listing in the Formulary. In the event the ministry is notified of the inability to supply the drug product at the time of listing or shortly thereafter the listing, the drug product may be removed (delisted) from the Formulary.

**j. Letter Confirming That No Rebates Were Provided**

The manufacturer must certify in writing that no rebates were provided to persons listed under subsection 12.1(1) of DIDFA with respect to the drug product from the time that Health Canada approved the product for sale in Canada.

6(1)(f) It is a condition for each strength and dosage form of a drug product to be designated as interchangeable with other products that the manufacturer of the drug product submit to the executive officer, certification in writing that no rebate as defined in subsection 12.1 (14) of the Act has been provided to a person listed in subsection 12.1 (1) of the Act with respect to the product contrary to the Act since Health Canada approved the product for sale in Canada;

6(1)(f) certification in writing that no rebate as defined in subsection 12.1 (14) of the Act has been provided to a person listed in subsection 12.1 (1) of the Act with respect to the product contrary to the Act since Health Canada approved the product for sale in Canada;

Subsection 12.1(14) of DIDFA defines “rebate” as including currency, a discount, refund, trip, free goods or any other prescribed benefit, but not including something provided in accordance with ordinary commercial terms that satisfies the conditions set out in subsection 2(3) of Regulation 935.
k. 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 proposed drug product submission. The ministry is not looking to enforce patent matters but rather to be made aware of any potential patent infringement prior to listing on the Formulary. The purpose of this requirement is for drug manufacturers to inform the Executive Officer any limitations in their NOCs. The ministry has, in the past, limited a listing of a drug based on patent restrictions noted in the NOC.

Please note that a manufacturer seeking for listing designation for its drug product must also disclose the current known patent status of the reference product and submit a letter which provides the following:

- a signed statement from the manufacturer stating that the submitted product, to its knowledge, does not infringe any patents;
- the name of the reference product;
- the medicinal ingredient;
- the strength;
- the drug identification number;
- the patent number; and
- the expiry date.

The letter must be dated and signed by a senior company official. Refer to the template letter in Part VII of the Guidelines.
I. Comparative Bioavailability Studies, Bioequivalence Data Checklist, Pharmacokinetic/Statistical Worksheet and master formulation of the test lot (biolot)

6(1) (h) It is a condition for each strength and dosage form of a drug product to be designated as interchangeable with other products that the manufacturer of the drug product submit to the executive officer, 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.

Manufacturers must satisfy this requirement by submitting the following:

- evidence of interchangeability (full reports of comparative bioavailability studies); and
- completed Bioequivalence Data Checklist; and
- completed Pharmacokinetic/Statistical Worksheet; and
- production master formulation for the biolot; and
- evidence of formulation proportionality for additional strength(s) of the dosage form, if applicable. Refer to subsection 6(4) of DIDFA Regulation for more details.

Similar / Comparable Dosage Forms Eligible for Interchangeability Evaluation

The submission filed under subsection 1.1(3) requires CED review. This is a non-streamlined submission even though Health Canada may have issued a declaration of equivalence (DoE) on the NOC.

Pursuant to subsection 1.1(3) of DIDFA, 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.
Under section 1.1(4) of DIDFA, “similar active ingredients” is defined to mean different salts, esters, complexes or solvates of the same therapeutic moiety. Be advised that different isomers will not be considered for interchangeability.

NOTE: Non-streamlined submissions filed under DIDFA must be reviewed by the CED. Exemption 6(7) does not apply. Refer to Part III-B.2.j. for more information.

The manufacturer must make a full submission as required under the DIDFA regulation including comparative bioequivalence data to the Ministry.

**Original Product (original/innovator)**

An “original product” is defined under Reg. 935 as the original source of a drug product in a particular strength and dosage form.

The ministry interprets **listed original product** to mean a listed brand name product (typically the innovator product), which has been approved by the ministry and listed on the Formulary as benefit.

Off-Formulary Interchangeability (OFI) means designating a drug product as interchangeable with an original product that is not listed in the Formulary.

For clarity and consistency, “original/innovator” will be used throughout the Guidelines.

**Evidence of the Formulation of 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 should 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.
Bioequivalence Data Checklist and Pharmacokinetic/Statistical Worksheet

The Bioequivalence Data Checklist and the Pharmacokinetic/Statistical Worksheet were developed based on the guidelines that CED reviewers use during their evaluation. They were designed to help manufacturers prepare submissions that are easy to review and ensure submissions proactively address the CED’s questions.

For each question on the Bioequivalence Data Checklist, manufacturers should provide short answers below the question and direct reviewers 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. A copy of the Bioequivalence Data Checklist and Pharmacokinetic/Statistical Worksheet is provided in Part VII of the Guidelines and on the ministry's website.

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).

At the time of submission, manufacturers are encouraged to provide supporting evidence, as required, to prevent delay in the submission review process. Submissions will be deemed incomplete and will remain as such until the ministry has been satisfied that a linkage has been sufficiently established between the various products referred to in the submission.
**Evaluation of Studies**

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

In the case of pharmacokinetic studies, the evaluation of interchangeability is generally based on three measures of bioavailability: AUC, Cmax, and Tmax.

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:

(a) t-test or ANOVA
(b) comparison of differences observed between means of the aforementioned measures (AUC, Cmax, and Tmax).

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

**Metered Dose Inhalers and Ophthalmic Suspensions and Other Drug Products**

If a comparative bioavailability study cannot be conducted (e.g., on drug products such as metered dose inhalers and ophthalmic suspensions), the ministry may consider comparative pharmacodynamic/clinical studies of the product requested for listing and the original/innovator 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) 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; and
(b) evidence the protocol was approved for safety and ethics by a qualified, independent review committee; and

(c) all resulting data and appropriate analyses in a form suitable for scientific review.

**Special Delivery Devices**

If the manufacturer is seeking interchangeability designation for a special delivery device (e.g. metered dose products, auto-injector pens or syringes, etc.), both comparative in-vitro and bioequivalence/clinical data are required. The submitted in-vitro data must demonstrate comparable performance of special delivery devices used to deliver the therapeutic drug substance.

Manufacturers must provide the following physiochemical comparative data:

- description, colour, clarity and expiry; and
- pH, viscosity, surface tension, specific gravity, distribution coefficient* (where applicable); and
- particle size distribution; and
- consistent drug content per drop; and/or
  - labelled potency claim per actuation; and
  - spray pattern (where applicable).

*Refer to section 6(5) of DIDFA for information on distribution coefficient test.

**Non-Aqueous Ophthalmic, Otic and Nasal Preparations**

If 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; and
- the amount of drug delivered per drop (the delivery systems must dispense consistent and comparable amounts); and
• distribution coefficient

*Refer to section 6(5) of DIDFA for information on distribution coefficient test

**Possible Exemptions**

Certain types of exemptions may be applicable depending on the drug submission type. Refer to the interpretation under each exemption for the specific criteria:

• This requirement may not apply to “pseudogeneric” drugs, as described in subsection 6(3) of the DIDFA Regulation.

• This requirement may not apply to additional strengths, as described in subsection 6(4) of the DIDFA Regulation.

• This requirement may not apply to drug products that are aqueous solutions, as described in subsections 6(5) and 6(5.1) of the DIDFA Regulation.

• This requirement may not apply to solid oral dosage form for systemic effect, as described in subsection 6(7) of the DIDFA Regulation.

A solid oral dosage form is any pharmaceutical preparation in a solid state for oral administration, e.g., tablet (chewable or not), granule, pellet, globule or capsule.

**Please Note**: These exemptions may not be applicable when a submission cross-references another listed interchangeable drug.

**m. Certification Confirming Product is Not a Private Label Product**

9. (1) A product that is a private label product shall not be designated as interchangeable. O. Reg. 221/10, s. 5.

   (2) In this section, “private label product” includes a drug product in respect of which,

      (a) the manufacturer applying for the designation of the product as a listed drug product does not directly fabricate the product itself, and
(i) is not controlled by a person that directly fabricates the product, or
(ii) does not control the person that directly fabricates the product, and
(b) either,

(i) the manufacturer does not have an arm’s-length relationship with a wholesaler, an operator of a pharmacy or a company that owns, operates or franchises pharmacies, or
(ii) the product is to be supplied under a marketing arrangement associating the product with a wholesaler or one or more operators of pharmacies or companies that own, operate or franchise pharmacies. O. Reg. 221/10, s. 5.

It is a condition that private label products are not eligible for designation under subsection 9 of the DIDFA.

The manufacturer must submit a letter confirming that the submitted drug product is not a private label product.

To assist manufacturers, the ministry has developed a template letter which is included in Part VII of the Guidelines and on the ministry’s website at:

PART III-B.2. REQUIREMENTS FOR SPECIFIC CASES (REGULATORY EXEMPTIONS)

a. Drug Product Approved Without Official Product Monograph

In cases where a drug product has been approved by Health Canada without an official product monograph (i.e., “old” drugs), the ministry will accept the information noted below as a product monograph in place of a Health Canada approved product monograph.

6(2) If Health Canada has not approved a product monograph for a drug product, the manufacturer of the product may, instead of submitting a copy of the product monograph as required under clause (1) (a), submit to the Executive Officer the following information:

1. Pharmaceutical information.
2. Information with respect to the product’s clinical pharmacology.
3. Information as to the product’s indications and clinical use.
4. A list of any contra-indications, warnings or precautions in the use of the product and of possible adverse reactions to its use.
5. A list of symptoms of an overdose of the product and information as to the treatment of an overdose.
6. Information with respect to the dosage and administration of the product.
7. Information regarding the availability of dosage forms for each strength of the product marketed in Canada.

Please review to the Therapeutic Products Directorate’s Guidance for Industry: Product Monograph for more detailed information.
b. **Pseudogeneric Drug Products**

Subsection 6(3) of the DIDFA Regulation allows the manufacturer to submit a “pseudogeneric” drug product without the CPID or master formulation and comparative bioavailability data.

6(3) Clauses (1) (c) and (h) do not apply to the manufacturer of a drug product if the dosage form, strength, formula and manufacturing process of the product and the testing standards for both the raw materials of the product and the finished product are identical to those of the product with which it seeks to be designated as interchangeable.

Pseudogeneric drug products are generic products made by the same manufacturer of the original/innovator product listed on the Formulary or listed as interchangeable on the OFI listing.

Generic product cross-referenced to another listed generic product does not qualify for the 6(3) exemption.

Pseudogeneric product submissions are streamlined.

This exemption applies only when the submitted drug product is **identical** to the “original/innovator product” with respect to physical and chemical properties, including:

- strength and dosage form;
- formulation including both active and inactive ingredients and their quantities;
- raw materials and finished product specifications;
- manufacturing processes;
- manufacturing site; and
- packaging format and size.
If a manufacturer of a drug product can satisfy the conditions outlined above, it will be exempt from clause 6(1) (c) (CPID or master formulation) and clause 6(1) (h) (comparative bioavailability клинических испытаний). The submission will not be forwarded to the CED for review.

Once deemed complete, the submission will proceed directly to the next stage of the review process. Be advised that a manufacturer must satisfy all applicable requirements under the DIDFA Regulations and the Guidelines in order for its submission to be deemed complete.

**Please Note:** This exemption does not apply to “cross-referenced” submissions where the submitted drug was approved by Health Canada on the basis of a reference to another generic drug product.

The NOC holder and the manufacturer of the original/innovator product should submit a letter, dated and signed by a senior company official, to confirm that the product is identical to the listed original/innovator product in all chemistry and manufacturing aspects except for markings and labelling.

**Other requirements:**
The submission must satisfy all other necessary requirements specified under DIDFA to complete the submission e.g. cross-licensing agreement letter, product confirmation letter, etc.
c. **Additional Strengths for Solid Oral Dosage Forms**

6(4) A manufacturer may satisfy the condition set out in clause (1) (h) for a strength of a drug product by submitting the evidence referred to in clause (1) (h) for another strength of the same dosage form of the drug product if that information is sufficient for the purposes of evaluating the interchangeability of both the strengths of the dosage form of the product.

This exemption applies to the additional strengths of **solid oral dosage forms** which are **proportional in formulation** to the strength assessed in the submitted bioavailability studies.

This exemption allows the comparative bioavailability/clinical data for one strength of a drug product to be considered to support other strengths of that product in the same dosage form. When a drug product does not qualify for this exemption, the manufacturer must submit separate comparative bioavailability/clinical studies for each strength of the drug product, including the master formulation for all strengths.

**Requirements**

Manufacturers who wish to use this exemption must provide master formulations of all strengths, including the production master formulation for the biolot.

d. **Suspensions, Emulsions or Oil-based Solutions**

Please note that a submission for drug products in the form of suspension, emulsions or oil-based solutions will not be streamlined (i.e. the submission must be forwarded to the CED for review and recommendation). This applies even in cases where Health Canada may have issued a declaration of equivalence (DoE) between the submitted product and the original/innovator product for the above dosage forms drug products.

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, the study design and endpoints should be justified.

e. Requirements for Non-Streamlined Aqueous Solutions

This subsection establishes the process and basis by which the ministry will accept a comparison of physicochemical data between a submitted drug and the listed original/innovator product in lieu of \textit{in vivo} bioequivalence data for the evaluation of interchangeability.

In the event that the manufacturer submits evidence that Health Canada has approved the use of a Non-Canadian Reference Product (NCRP) in pharmaceutical equivalence study, and has issued an NOC the NCRP policy and requirements must be met (refer to Part II-B.2.i).

Although the ministry has adapted Health Canada's submission requirements for certain routes of administration for aqueous solutions, the manufacturer is required to provide additional comparative test parameter in order for the products to be considered as pharmaceutically equivalent to the original/innovator drug product.

The ability of the drug to partition between the drug solution at its observed pH and an octanol phase is a test which directly demonstrates pharmaceutical equivalence for a solution. The \textit{DISTRIBUTION COEFFICIENT} test evaluates the partitioning between the aqueous solution at the pH of the product and octanol.

\textit{DISTRIBUTION COEFFICIENT} test is required for ophthalmic, nasal and otic formulations. It is not needed for oral or IV solutions.

The distribution coefficient can be determined as follows:

Mix equal volumes of undiluted ophthalmic solution and octanol. Agitate to allow distribution of the drug between the two phases and measure the concentration of the drug in each phase using a suitable analytical method. \( DC = \frac{\text{concentration in octanol}}{\text{concentration in water}} \). Test must be comparative.
6(5) Clause (1) (h) does not apply with respect to a drug product that is pharmaceutically equivalent to the original product, demonstrates the same physicochemical properties of the original product, is the same dosage form, packaging format and strength as the original product and is one of the following:

1. A parenteral aqueous solution, or a powder for reconstitution into an aqueous solution, that may be administered in an intravenous, intramuscular, subcutaneous or intrathecal fashion and that is in the same solvent and in the same concentration as the original product.

2. An oral solution, elixir, syrup or other similar solubilized form in the same concentration as the original product and which contains no ingredient that will affect the bioavailability of the active ingredient.

3. An ophthalmic, otic, nasal, rectal, vaginal or inhaled solution that is topical and aqueous.

This exemption does not apply to suspensions, emulsions, or oil-based injections or solutions and dermatological products. Refer to Part III-B.2.d. for bioavailability or bioequivalence study requirements.

This exemption may be applied to non-aqueous oral solutions (i.e., alcohol co-solvent solutions) described in paragraph 2 of subsection 6(5) of the DIDFA Regulation.

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

For aqueous solutions, and non-aqueous solutions described in paragraph 2 of subsection 6(5), the strength, dosage form, and packaging format must be identical and the container and closure should be similar in form and material to that of the listed original/innovator product. For example, a product in an ampoule will not be considered for designation of interchangeability with the original/innovator product in a vial.

Please Note: If Health Canada has issued a declaration of equivalence (DoE) in respect of an aqueous solution product on/after February 15, 2005, that product will be deemed to be pharmaceutically equivalent and to have met the physicochemical equivalence requirements described above. Please see subsection 6(5.1) of the DIDFA Regulation.
Physicochemical Evaluation Criteria

The ministry now accepts Health Canada’s *Guidance for Industry: Pharmaceutical Quality of Aqueous Solutions* (February 15, 2005) as the guidance document for the evaluation of physicochemical data of these products except for the test requirement for DISTRIBUTION COEFFICIENT indicated above.

Health Canada’s guidance on aqueous solutions outlines the test parameters requirement so that the ministry can assess the submitted product on the basis of pharmaceutical equivalence. In cases where Health Canada has not evaluated an aqueous solution to be equivalent to the listed original/innovator drug product, additional information may be requested by the ministry to facilitate the evaluation. Manufacturers must comply with these requests in order to facilitate the review and expedite the review process.

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 or the submission will be deemed incomplete.

Testing Specifications

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).

Tests performed on drug products more than one year as of the date of submission may be accepted if the manufacturer confirms the formulations are the same by providing the CPIDs or the master formulations of the submitted products.
For more detailed information on testing parameters and finished product specifications, please refer to the following documents, which may be accessed at: http://www.hc-sc.gc.ca

- Good Manufacturing Practices
- Draft Guidance for Industry, Quality (Chemistry and Manufacturing), Health Product and Food Branch Guidance Document,
## DRUG SUBMISSION REQUIREMENTS CHECKLIST FOR AQUEOUS SOLUTIONS*

*adapted from Health Canada’s *Pharmaceutical Quality of Aqueous Solutions (2005)*

<table>
<thead>
<tr>
<th>Drug Product Information</th>
<th>Reference Product Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug product: product name (chemical name/ strength/ dosage form)</td>
<td>Reference product: product name (chemical name/ strength/ dosage form)</td>
</tr>
<tr>
<td>Lot number:</td>
<td>Lot number:</td>
</tr>
<tr>
<td>Expiry date:</td>
<td>Expiry date:</td>
</tr>
<tr>
<td>Package size:</td>
<td>Package size:</td>
</tr>
</tbody>
</table>

### Testing Parameter

<table>
<thead>
<tr>
<th>Universal Tests (generally applicable to all dosage forms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description, colour, clarity, expiry</td>
</tr>
<tr>
<td>Assay (drug substance), Potency</td>
</tr>
</tbody>
</table>

### Specific Tests (specific to individual dosage forms)

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbial Limits (USP &lt;61&gt;) (if product is not sterile)</td>
<td>S</td>
<td>N/A</td>
<td>S</td>
<td>S (multi use)</td>
<td>S (multi use)</td>
<td>N/A</td>
</tr>
<tr>
<td>Uniformity of Dosage Units</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------</td>
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<tr>
<td>UNIVERSAL TESTS (generally applicable to all dosage forms)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>(USP &lt;905&gt;) (if packaged in a single-unit container)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Delivered Dose Uniformity (USP &lt;601&gt;) (if packaged with a device for delivery)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>S, C</td>
<td>S, C</td>
<td>N/A</td>
</tr>
<tr>
<td>Antimicrobial Preservative Content (if present)</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Antimicrobial Preservative Effectiveness (if present) (USP &lt;51&gt;)</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Potency, Salt, Solvent</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Viscosity (USP &lt;911&gt;)</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Specific Gravity or Density (USP &lt;841&gt;)</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Osmolality (mol/kg) / Osmolarity (mol/L) (if tonicity is declared on the product labelling) (USP &lt;785&gt;)</td>
<td>N/A</td>
<td>S,C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>S,C</td>
</tr>
<tr>
<td>Surface Tension</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Buffering Capacity (if product contains a buffer)</td>
<td>D,C</td>
<td>D,C</td>
<td>D,C</td>
<td>D,C</td>
<td>D,C</td>
<td>D,C</td>
</tr>
<tr>
<td>Particulate Matter (USP &lt;788&gt; / &lt;789&gt;)</td>
<td>N/A</td>
<td>S</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>S</td>
</tr>
<tr>
<td>Sterility (if sterility is declared on the product)</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
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</tr>
<tr>
<td><strong>UNIVERSAL TESTS (generally applicable to all dosage forms)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Labelling (USP &lt;71&gt;)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial Endotoxins / Pyrogens (USP &lt;85&gt; / USP &lt;151&gt;)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>S</td>
</tr>
<tr>
<td>Distribution Coefficient</td>
<td>N/A</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>CONTAINER CLOSURE SYSTEM TESTS</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Deliverable Volume, Minimum Fill, or Volume for Injection (if applicable) (USP &lt;698&gt;, USP &lt;755&gt;, or USP &lt;1&gt;)</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>D</td>
<td>D</td>
<td>S</td>
</tr>
<tr>
<td>Droplet Size or Volume (if administered as drops)</td>
<td>D,C</td>
<td>D,C</td>
<td>D,C</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Droplet Size Distribution (if administered as a spray)</td>
<td>D,C</td>
<td>D,C</td>
<td>D,C</td>
<td>D,C</td>
<td>D,C</td>
<td>N/A</td>
</tr>
<tr>
<td>Device Attributes (if applicable)</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D,C</td>
<td>D,C</td>
<td>D</td>
</tr>
</tbody>
</table>

S = generally included in the finished product release specifications
D = generally performed during pharmaceutical development
C = generally included in a comparative study of the physicochemical properties
N/A = not applicable or not required

*Orally administered solutions may be either aqueous or alcohol-based; all other solutions, regardless of the route of administration, must be aqueous.
f. Streamlined Aqueous Solutions

The exemption provided in subsection 6(5.1) of the DIDFA Regulation applies only to selective routes of administration of aqueous solution products in respect of which Health Canada has issued a declaration of equivalence (DoE) on or after February 15, 2005.

6(5.1) For the purposes of subsection (5), if a drug product has been designated by Health Canada on/after February 15, 2005 as equivalent to the original product or to another listed interchangeable product with which it would be designated as interchangeable, the drug product shall be deemed to be pharmaceutically equivalent to the original product and to demonstrate the same physicochemical properties of the original product.

This exemption does not apply to suspensions, emulsions, or oil-based injections or solutions and dermatological products. Refer to Part III-B.2.d. for bioavailability or bioequivalence study requirements.

This exemption may be applied to non-aqueous oral solutions (i.e., alcohol co-solvent solutions) described in paragraph 2 of subsection 6(5) of the DIDFA Regulation.

For aqueous solutions, and non-aqueous solutions described in paragraph 2 of subsection 6(5), the strength, dosage form, and packaging format must be identical and the container and closure should be similar in form and material to that of the listed original/innovator product. For example, a product in an ampoule will not be considered for designation of interchangeability the original/innovator product in a vial.

The ministry will accept Health Canada’s DoE for selective routes of administrative (oral, ophthalmic, otic, nasal, inhalation and injection) for aqueous solutions when making an evaluation of interchangeability, provided that:

- equivalence is declared on the Notice of Compliance (NOC), and the NOC was issued on/after February 15, 2005, following the publication of Health Canada’s guidance document *Pharmaceutical Quality of Aqueous Solutions*; the reference product is:
o identical to the listed original/innovator product,
o a non-Canadian reference product, approved under Health Canada’s Non Canadian Reference Product policy (refer to Part III-B.2.i), or
o another listed interchangeable product with which it would be designated as interchangeable, if the original/innovator product is no longer marketed.

Please note that preservative-containing vs. preservative-free interchangeability assessment is a “non-streamlined” process, where in-vitro data to demonstrate pharmaceutical equivalence is required for the submission, and the submission will be reviewed by the CED even though the product may be exempt from clause 6 (1) (h) of the DIDFA Regulation.

If this exemption does not apply, the manufacturer must satisfy all the requirements specified in subsection 6 (1)(h) of the DIDFA Regulation.

Note that the requirements under clause 6(1) (c) of the DIDFA Regulation must continue to be satisfied for all aqueous solution submissions, including those that qualify under subsection 6(5.1). That is, a completed CPID (or master formulation) must be submitted.

g. Product Designated as Equivalent to the Original/Innovator Product by Health Canada

The ministry will accept Health Canada’s declaration of equivalence (DoE) as meeting the requirement under clause 6(1) (c) for all products except aqueous solutions described in subsections 6(5) of the DIDFA Regulation.

6(6) Clause (1) (c) does not apply with respect to a product that has been designated by Health Canada as equivalent to the original product or to another listed interchangeable product with which it would be designated as interchangeable unless the product is described in subsection (5).

This is possible where:
  - equivalence is declared on the Notice of Compliance; and
the reference product is:
  - identical to the listed "original/innovator product", or,
  - a non-Canadian reference product, approved under Health Canada’s Non-Canadian Reference Product policy ((refer to Part III-B.2. i), or,
  - another listed interchangeable product with which it would be designated as interchangeable, if the listed "original/innovator product" is no longer marketed.

Please Note: In the case of cross-referenced submissions, the CPID will be required for both the listed drug product and the cross-referenced drug product. In addition, bioequivalence data is required for the cross-referenced product. Refer to subsection 6(1) of the DIDFA Regulation for more information.

When more than one strengths of the same dosage form is submitted for listing, subsection 6(4) of the DIDFA Regulation may apply. The CPID or documentation disclosing the master formulation for each strength must be provided as evidence of proportionality of the product composition.

h. Streamlined Solid Oral Dosage Forms

The ministry has fully harmonized with Health Canada’s review processes as they relate to the review of solid oral dosage forms for systemic effect.

The ministry will rely entirely on Health Canada’s declaration of equivalence (DoE) for the purpose of determining the interchangeability of these products.

6(7) Clause (1) (h) does not apply to a product that is a solid oral dosage form for systemic effect and that has been designated by Health Canada as equivalent to the original product or to another listed interchangeable product with which it would be designated as interchangeable.

This is possible where:
- equivalence is declared on the Notice of Compliance; and
- the reference product is:
identical to the listed original/innovator product, or,

- a non-Canadian reference product, approved under Health Canada's Non-Canadian Reference Product policy (refer to Part III-B.2.i ), or,

- another listed interchangeable with which it would be designated as interchangeable, if the original/innovator product is no longer marketed (Refer to Part II-B.2.k for more information).

If this exemption does not apply, the manufacturer must satisfy all the requirements specified in clause 6(1) (h) of the DIDFA Regulation.

A solid oral dosage form is any pharmaceutical preparation in a solid state for oral administration, e.g., tablet (chewable or not), granule, pellet, globule or capsule.

Pursuant to section 1.1(3) of DIDFA, the Executive Officer may consider making an interchangeability designation in respect of products containing a drug or drugs in the same amounts of the same or similar active ingredients in the same or similar dosage form

Under section 1.1(4) of DIDFA, “similar active ingredients” is defined to mean different salts, esters, complexes or solvates of the same therapeutic moiety. Be advised that different isomers will not be considered for interchangeability.

NOTE: Submissions for solid oral dosage forms for systemic effect and certain aqueous solutions that have been declared as equivalent with an original/innovator product, but contain similar active ingredients and similar dosage forms as the original/innovator product will not be streamlined and will be reviewed by the CED.

i. Non-Canadian Reference Products

A “Canadian Reference Product” means a drug in respect of which Health Canada has issued a Notice of Compliance 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. Please refer to the Therapeutic Products Directorate: Preparation of Drug Submissions document for further information.

The ministry will only accept a Non-Canadian Reference Product (NCRP) as equivalent to the Canadian Reference Product if that NCRP conforms to the criteria established by, and has been
approved by, Health Canada. In addition, the Canadian Reference Product must be recognized by the ministry as the original/innovator product.

**Solid Oral Dosage Forms**

In the event that the manufacturer submits evidence that Health Canada has approved the use of a NCRP in the comparative bioavailability or comparative clinical study, and has issued an NOC the following requirements must be met:

1. If the NOC has a declaration of equivalence (DoE) from Health Canada to a NCRP that has the SAME product name and SAME manufacturer as the Canadian reference product (CRP), the manufacturer must:
   
   i. indicate that a NCRP was used on the cover letter

2. If the NOC has no declaration of equivalence (DoE) from Health Canada to a NCRP that has the SAME product name and SAME manufacturer as the Canadian reference product, the manufacturer must:
   
   i. indicate that a NCRP was used in the comparative bioavailability or comparative clinical study; and

   ii. provide justification as to why a NCRP was used on the cover letter.

3. If the NOC has declaration of equivalence (DoE) from Health Canada to a NCRP that has a DIFFERENT product name or DIFFERENT manufacturer as the Canadian reference product, the manufacturer must:
   
   i. indicate that a NCRP was used in the comparative bioavailability or comparative clinical study;

   ii. provide justification as to why a NCRP was used on the cover letter; and

   iii. submit the dissolution profile data between the CRP and the NCRP, as required by Health Canada’s policy and requirements for NCRP.
4. If the NOC has no declaration of equivalence (DoE) from Health Canada to a NCRP that has a DIFFERENT product name or DIFFERENT manufacturer as the CRP product, the manufacturer must:

i. indicate that a NCRP was used in the comparative bioavailability or comparative clinical study;

ii. provide justification as to why a NCRP was used is required on the cover letter; and

iii. submit the dissolution profile data between the CRP and the NCRP, as required by Health Canada’s policy and requirements for NCRP.

**Aqueous Solutions**

The conditions listed below apply to non-streamlined and streamlined aqueous solutions where NCRP has a DIFFERENT product name or DIFFERENT manufacturer as the CRP product.

1. For aqueous solutions, as classified under the *Health Canada Guidance for Industry*, the manufacturer must:

i. submit a waiver of comparative bioavailability studies for oral solutions, as applicable;

ii. submit a waiver of the requirement to demonstrate in vivo bioequivalence for aqueous solutions, as applicable;

iii. provide proof of purchase of the Canadian reference Product;

iv. provide a certificate of analysis, i.e., the results of comparative and non-comparative physiochemical parameter tests with the innovator (reference product) demonstrating pharmaceutical equivalence. This includes product name, strength dosage form and package format (if applicable) and the expiry date of the test and reference product;

v. describe any device attributes, as required by Health Canada; and

vi. indicate that a NCRP was used; and if the submission is for a non-streamlined product, justification as to why a NCRP was used is required on the cover letter.
Other Dosage Forms

The conditions listed below apply to other dosage forms that are non-streamlined submissions.

In the event that the manufacturer submits evidence that Health Canada has approved the use of a Non-Canadian Reference Product (NCRP) in the comparative bioavailability or comparative clinical study, or pharmaceutical equivalence study, and has issued an NOC the following requirements must be met:

i. submit a comparative clinical /bioequivalence study or physiochemical study as required between the reference products, by Health Canada for NCRP, between the reference products; and

ii. indicate that a NCRP was used and if the submission is for a non-streamlined product, justification as to why a NCRP was used is required in the cover letter.

The ministry may ask for further documentation if the ministry determines, in its sole discretion, that there is insufficient linkage between the CRP and the NCRP.

j. Comparable Dosage Form and Similar / Same Medicinal Ingredients and Different Salts

Pursuant to section 1.1(3) of DIDFA, the EO may consider making an interchangeability designation in respect of products containing a drug or drugs in the same amounts of the same or similar active ingredients in the same or similar dosage form

Under section 1.1(4) of DIDFA, “similar active ingredients” is defined to mean different salts, esters, complexes or solvates of the same therapeutic moiety.

Be advised that different isomers will not be considered for interchangeability.

A full submission that meets the requirements set out in section 6 of the DIDFA Regulation is required. In addition, the manufacturer must submit the comparative clinical or bioequivalence data for CED review and recommendation. If necessary, please contact the ministry for the requirements for submission for similar dosage forms or similar active ingredients.
**Note:** Submissions for products seeking to be designated as interchangeable with original/innovator products, but contain similar active ingredients and/or similar dosage forms as the original/innovator product will not be streamlined and will be reviewed by the CED.

For better clarity, although Health Canada may have issued a declaration of equivalence (DoE) on the NOC, in this circumstance, the submission will not be streamlined (i.e. the submission must be forwarded to the CED for review and recommendation).

**k. Original Product No Longer Listed and Discontinued Drug Products**

The ministry will accept submissions for a designation of interchangeability with an original/innovator product that was, but is no longer, listed on the Formulary as a benefit (e.g. products that have been discontinued or delisted at the request of the manufacturer).

**Please Note:**

The ministry will not accept multiple source submissions for consideration of interchangeability designation and/or benefit listing if the original/innovator product was delisted due to clinical concerns e.g. safety or toxicity. A generic product will only be considered for interchangeability and benefit designations when the clinical concerns have been addressed. The manufacturer must provide clinical study/data that addresses the related clinical concerns to the CED for review and recommendation.

For clarification on the reason(s) for delisting, please contact Ontario Public Drug Programs.

If a manufacturer is seeking a designation of interchangeability with an original/innovator product that was but is no longer listed on the Formulary, the cover letter accompanying the submission must indicate the specific Formulary edition, supplement (where applicable), and page number indicating when the original/innovator product was listed. Manufacturers must provide a copy of the previous listing in order to avoid a delay in the review process.

If a manufacturer is seeking to have its product (“Submitted Product”) designated as interchangeable with an original/innovator product that has been discontinued (“Original/Innovator Product”), a Health Canada declaration of equivalence (DoE) between the Submitted Product and a currently listed generic product (“Listed Generic”) in the Formulary will be sufficient to establish equivalence between the Submitted Product and the Original/Innovator Product.
The ministry will not consider generic-to-generic comparisons for interchangeability unless the generic reference product is designated as interchangeable with the “original/innovator product” in the Formulary and the original/innovator product is discontinued and no longer available.
I. Dermatological Products

(7.1) Clause (1) (h) does not apply to a dermatological product that contains one or more glucocorticoids as the only active ingredient or ingredients and that has been designated by Health Canada as equivalent to the original product or to another listed interchangeable product with which it would be designated as interchangeable. O. Reg. 285/15, s. 1 (2).

Certain dermatological drug products are exempt from the in vivo bioequivalence study requirement in section 6(1)(h). To qualify for the exemption the product must contain one or more glucocorticoids as the only active ingredient(s), and have a declaration of equivalence (DoE) from Health Canada with the original product or another listed interchangeable product with which it would be designated as interchangeable.

The manufacturer should clearly identify in the submission that the submitted product is a glucocorticoids drug product.

Non-glucocorticoids drug products without DoE must comply with the in vivo bioequivalence study requirement according in section 6(1)(h) of Reg 935 of DIDFA.

m. Transdermal Route of Administration for Systemic Effect Drug Products

(7.2) Clause (1) (h) does not apply to a product with a transdermal route of administration for systemic effect that has been designated by Health Canada as equivalent to the original product or to another listed interchangeable product with which it would be designated as interchangeable. O. Reg. 285/15, s. 1 (2).

Drug products with a transdermal route of administration for systemic effect are exempt from the in vivo bioequivalence study requirement in clause 6(1)(h). To qualify for the exemption the product must have a declaration of equivalence (DoE) from Health Canada with the original product or another listed interchangeable product with which it would be designated as interchangeable.
The manufacturer should clearly identify in the submission that the submitted product is a transdermal route drug product for systemic effect.

Transdermal drug products without DoE must comply with the in vivo bioequivalence study requirement according in section 6(1)(h) of Reg 935 of DIDFA.
To maintain a product interchangeability listing on the Formulary, the manufacturer must comply with the conditions listed below.

8. (1) The following conditions must be met in order for a drug product that has been designated as interchangeable to continue to be designated as interchangeable:

1. The manufacturer of the product shall give the executive officer notice of any change made to the product, including a formulation change, and of any change in the ownership of the manufacturer.

2. The product must be authorized for sale under the *Food and Drugs Act* (Canada).

3. The manufacturer of the product must continue to be able to supply the product at the drug benefit price in a quantity that is sufficient to meet the demand for the product where the product is designated as a listed drug product under the *Ontario Drug Benefit Act*.

4. If the product is a listed drug product under the *Ontario Drug Benefit Act*, the manufacturer shall not sell the product at a price higher than the drug benefit price permitted under that Act whether or not the product is supplied for the purposes of that Act.

5. Revoked: O. Reg. 221/10, s. 4 (3).

5.1, 5.2 Revoked: O. Reg. 221/10, s. 4 (1).

6. Revoked: O. Reg. 221/10, s. 4 (3).

7. If the drug product has not been designated as a listed drug product under the *Ontario Drug Benefit Act*, the manufacturer of the product shall give the executive officer notice of every change in the manufacturer’s list price for the drug product.

8. The manufacturer must not have provided a rebate as defined in subsection 12.1 (14) of the Act to a person listed in subsection 12.1 (1) of the Act with respect to the product contrary to the Act since Health Canada approved the product for sale in Canada.
9. If required by the executive officer, the manufacturer of a product that has been designated as interchangeable shall inform the executive officer of the price that the manufacturer receives for the product, net of the value of any ordinary commercial terms. O. Reg. 28/97, s. 3; O. Reg. 458/06, s. 5 (1-4); O. Reg. 558/06, s. 3 (1, 2); O. Reg. 321/07, s. 2 (1-4); O. Reg. 354/08, s. 2 (1-3); O. Reg. 221/10, s. 4 (1-4); O. Reg. 221/10, s. 4 (5).

(2) For greater certainty, the conditions set out in subsection (1) apply whether the designation of the product as an interchangeable product took place before, on or after July 1, 2010. O. Reg. 458/06, s. 5 (5); O. Reg. 221/10, s. 4 (6).

(3) Revoked: O. Reg. 221/10, s. 4 (7).

(4) Revoked: O. Reg. 221/10, s. 4 (9).

Paragraph 1 of subsection 8(1) of the DIDFA Regulation require that manufacturers notify the ministry of changes made to a listed drug product, including a formulation change, and of any change in the ownership of the manufacturer. Without limiting the generality of the foregoing, the ministry must also be notified of changes to a product’s DIN and significant changes to the product monograph.

Please refer to Health Canada Levels I and II categories of guidance “Post-Notice of Compliance (NOC)-Quality Guidance Appendix 1 for Human Pharmaceuticals”

Often manufacturers provide general notice of change letters without identifying the listed products affected by the change. To facilitate processing, manufacturers should clearly indicate which products are affected by the change, and should not include products that are currently not funded through OPDP. The ministry may return a non-specific list to manufacturers to identify the affected products before it proceeds in assessing the change.

Paragraph 2 of subsection 8(1) requires that for a drug product to continue to be designated as an interchangeable product, the manufacturer of the product must comply with Health Canada’s requirements, including having a valid NOC and/or DIN and be authorized for sale under the Food and Drugs Act (Canada).
Paragraph 8 of subsection 8(1) requires a manufacturer to ensure that no rebate is provided to a person listed in subsection 12.1(1) of the DIDFA with respect to the drug product from the time that Health Canada approved the product for sale in Canada.

In addition to the above, if the interchangeable product is listed as a benefit under the ODBA, the additional conditions set out in section 12.1 of the ODBA must also be met.
A generic drug manufacturer may seek a price exception for its proposed interchangeable product that is less than or equal to 50% of the Drug Benefit Price (DBP) of the original/innovator product (brand) provided that it meets all the requirements under subsection 11(7) of O. Reg. 201/96 made under the *Ontario Drug Benefit Act*. The ministry may consider a request for the exception if the manufacturer meets the following regulatory requirements:

- the interchangeable product is proposed for designation as a listed drug product on the Ontario Drug Benefit Formulary/Comparative Drug Index (the “ODB Formulary”) on or after April 1, 2012

- the interchangeable product proposed for listing has not been previously designated as a listed drug product on the ODB Formulary at any other time

- the manufacturer represents and warrants that the manufacturer, or another manufacturer of a product that is interchangeable with the original/innovator product, has successfully challenged the patent(s) of the original/innovator product with the result that the manufacturer’s product can be sold in Canada earlier than if the patent(s) had expired or if the challenge had not been brought. In support of this representation and warranty, the manufacturer submits to the Executive Officer evidence confirming the expiry date of the patent(s) of the original/innovator product and documents, including file numbers or citations of court decision(s), confirming that a court of competent jurisdiction has either:
  
  - dismissed an application brought under subsection 6(1) of the *Patented Medicines (Notice of Compliance) Regulations* in response to a Notice of Allegation served by the Manufacturer or another manufacturer relating to the patent(s) of the original/innovator product, on one of the following grounds:

    - the allegation that the patent(s) is invalid is justified;
- the allegation that the statement made under paragraph 4(4)(d) of the *Patented Medicines (Notice of Compliance) Regulations* is false is justified; or

  o pursuant to subsection 60(1) of the *Patent Act*, declared that the patent(s) of the original/innovator product is invalid.

- the manufacturer has not entered into any arrangement, other than a cross-licensing agreement, with the manufacturer of the original/innovator product with respect to the product that is proposed for designation as a listed drug product, including any first-to-market arrangement or delayed-entry arrangement.

For interchangeable drug products that meet the above regulatory requirements, the manufacturer must agree that the exception set out in subsection 11(7) of O. Reg. 201/96 will cease to apply three months (90 calendar days*) after the first product of any manufacturer that is interchangeable with the original/innovator product becomes a listed drug product, at which time the drug benefit price of the product shall revert to a price that is less than or equal to 25% (or 35% in the case of a drug product that is not a solid dosage form) of the drug benefit price of the original/innovator product as set out in the Formulary on the date that the product was first proposed for designation as a listed drug product.

*Note:* In cases where the 90th day does not fall on the effective date of an update to the Formulary, the exception will be deemed to no longer apply on the effective date of the Formulary update that immediately follows the end of the 90 days.

The ministry has developed a standard template for manufacturers to complete, which is available on the ministry website at:

PART III-B.5. NOTIFICATION OF CHANGE TO THE LISTED DRUG PRODUCT

Paragraph 1 of subsection 8(1) of the DIDFA Regulation requires that manufacturers notify the ministry of changes made to a listed drug product, including a formulation change, and of any change in the ownership of the manufacturer. Without limiting the generality of the foregoing, the ministry must also be notified of changes to a product’s DIN and significant changes to the product monograph.

Please refer to Health Canada Levels I and II categories of guidance categories noted in “Post-Notice of Compliance (NOC)-Quality Guidance Appendix 1 for Human Pharmaceuticals”

8. (1) The following conditions must be met in order for a drug product that has been designated as interchangeable to continue to be designated as interchangeable:

1. The manufacturer of the product shall give the executive officer notice of any change made to the product, including a formulation change, and of any change in the ownership of the manufacturer.

The ministry requires manufacturers to submit notification of changes for Level I and II categories. In addition the following types of change (other than Levels I & II) must also be reported to the ministry to maintain listing of the drug products:

- change in ownership
- change in DIN
- change in company name
- change in drug product name
- change in product monograph
Manufacturers must report changes for Level I & II and the above additional listed types of change to its listed drug products within 30 days of the receipt of approval from Health Canada. A Notice of Change submission must be completed within this timeframe. Each notification of change must be dated and signed by a senior company official.

Manufacturers should clearly indicate which products are affected by the change. Manufacturers should not include those products that are currently not funded through OPDP for notification of change. The ministry will only acknowledge those products listed in the Formulary. The ministry may return the list to manufacturers to identify the affected products before it proceeds in assessing the change. A separate notification submission is required for each drug.

Justification/rationale should be provided where certain information is not available, otherwise the submissions will be deemed as incomplete.

To simplify administrative changes, a maximum of ten drug products of the same drug substance per submission is suggested as a guideline.

The following changes must be reported to the ministry in order for an interchangeable product to continue to be designated as interchangeable on the Formulary.

a. Change in DIN, Ownership, Company Name and Drug Product Name

- Signed & dated covering letter on company letterhead that includes:
  
  a) The type of notification (i.e. level of change);
  b) Narrative of the change(s);
  c) A brief rationale for the change(s);
  d) Listing of all drug products, including the DIN(s), which are affected by the change(s), and if available, a reference to Drug Submission Master File Number and Product File Number;
  e) Confirmation that the master formulation has not changed; and
  f) Confirmation that the bioavailability has not been affected.
 Evidence that Health Canada has approved the change:

a) Notice of Compliance (NOC) and/or No Objection Letter (NOL); and

   I. Where No Objection Letter is not available, provide linkage information such as email correspondence with Health Canada

b) Completed, dated and signed Drug Notification Form (DNF) reflecting the old and new changes (as applicable): DIN, manufacturer name, company name or drug product name and for each drug product affected

- Updated product monograph (annotated/tracked and non-annotated) with most recent date of revision.

b. Changes to the Product Monograph

For changes to product monograph where the bioavailability has been affected, a submission including the new comparative bioequivalence/clinical study is required. Refer to guidelines for the appropriate submission requirements.

Only significant changes to the product monograph must be brought to the attention of the ministry. Significant changes include any changes to indications, significant changes to contraindications, adverse effects, dosage regimen, and warning/precautions.

- Signed & dated covering letter on company letterhead that includes:

  a) The type of notification (i.e. level of change);
  b) Narrative of the change(s);
  c) A brief rationale for the change(s);
  d) Listing of all drug products, including the DIN(s), which are affected by the change(s)

- Evidence that Health Canada has approved the change:

  a) Notice of Compliance (NOC) and/or No Objection Letter (NOL);
  b) Where No Objection Letter is not available, provide linkage information such as email correspondence with Health Canada.
- Updated product monograph (annotated/tracked and non-annotated) with the date of revision

- Additional linkage information that Health Canada has approved the change e.g. new cross-licensing agreement.

**Note:** For Level III changes where Health Canada has not issued an NOC, or No Objection Letter and/or updated product monograph the following supporting information is required:

i. Manufacturer must confirm that the product is a Level III notification of change as per Health Canada’s Post NOC Changes Notice;

ii. Evidence showing the product meeting Level III criteria & conditions as per Health Canada’s Post NOC Changes Notice. Print and submit a copy of criteria & conditions corresponding to the changes made to the submitted product;

iii. A copy of correspondence (letter or email) between Manufacturer and Health Canada regarding notification of change, if available;

iv. Evidence that the changes have been approved internally by the company is required. The manufacturer is required to provide an internal approval form of the changes or “change control document”. The approval form/form must contain the product information-DIN, product name, strength, dosage form, package format, size, nature of change, reference document, implemented by (signed and dated) and approved by (signed and dated); and

v. A copy of the annual notification of change, if applicable.

**b.1. Changes to generic Product Monograph matching Innovator PM**

When a manufacturer notifies the ministry that the PM of a generic product has been updated to match the innovator’s PM, the ministry will review changes and determine if the notification is complete or incomplete.

The ministry **will no longer** issue a confirmation letter for the complete submission. The manufacturers **will only** be asked to respond to the Branch if additional information is required to complete the submission. That is an incomplete letter will be issued to the manufacturers.
This change in communication process applies ONLY to all current and future multiple source submissions for the notice of change in the PM to match the innovator PM.

Please be advised that the manufactures must continue to provide any notification of change to meet the conditions set out in section 8 of the Drug Interchangeability and Dispensing Fee Act (DIDFA) Regulation in order to continue to be designated as interchangeable drug product.

c. **Changes in the Master Formulation**

1. For minor changes in the master formulation where the bioavailability is not affected, the notification should include:

   - Signed & dated covering letter on company letterhead that includes:
     a) The type of notification (i.e. level of change);
     b) Narrative of the change(s);
     c) A brief rationale for the change(s);
     d) Listing of all drug products, including the DIN(s), which are affected by the change(s);
     e) Confirmation that the master formulation has changed;
     f) Old and new master formulation (CPID);
     g) List all changes made to the master formulation and indicate percent (%) changes in the quantity of the ingredient; and
     h) Confirmation that the bioavailability has not been affected;

   - Evidence that Health Canada has approved the change:
     a) Notice of Compliance (NOC) and/or No Objection Letter (NOL)
     b) Where No Objection Letter is not available, linkage information such as email correspondence with Health Canada; and

   - Old and new DNF reflecting the old and new DINs for the drug product, clearly identifying the strengths and dosage forms affected by the change (if applicable); and
• Updated product monograph (annotated/tracked and non-annotated) with the date of revision and control number; and

• Additional linkage information that Health Canada has approved the change e.g. new cross-licensing agreement.

2. For major changes in the master formulation (i.e., changes which may affect the bioavailability of the product) the notification should include:

• Signed & dated covering letter on company letterhead that includes:
  a) The type of notification (i.e. level of change);
  b) Narrative of the change(s);
  c) A brief rationale for the change(s);
  d) Listing of all drug products, including the DIN(s), which are affected by the change(s);
  e) Confirmation that the master formulation has changed;
  f) Old and new master formulation (CPID); and
  g) List all changes made to the master formulation and indicate percent (%) changes in the quantity of the ingredient.

• Evidence that Health Canada has approved the change:
  a) Notice of Compliance (NOC) and/or No Objection Letter (NOL);
  b) Where No Objection Letter is not available, linkage information such as email correspondence with Health Canada; and
  c) Old and new DNF reflecting the old and new DINs for the drug product, clearly identifying the strengths and dosage forms affected by the change (if applicable).

• Updated product monograph (annotated/tracked and non-annotated) with the date of revision; and

• A new comparative bioavailability study.
Refer to clause 6(1)(h) of Regulation 935 under the *Drug Interchangeability and Dispensing Fee Act* for more information on bioavailability evidence.

d. Changes Not Approved by Health Canada and Other Changes

If Health Canada has not approved the change (i.e., “old” drugs), the manufacturer should submit documentation to support the new changes:

- Signed & dated covering letter on company letterhead that includes:
  
a) The type of notification (i.e. level of change if available);
  
b) Narrative of the change(s);
  
c) A brief rationale for the change(s);
  
d) Listing of all drug products, including the DIN(s), which are affected by the change(s);
  
e) Confirmation that the master formulation has/has not changed; and
  
f) Confirmation that the bioavailability has/has not been affected.

- Evidence that Health Canada has previously approved the original product:
  
a) Original Notice of Compliance (NOC) ; and
  
b) Original Completed Drug Notification Form (DNF) dated and signed

- Old and new master formulation (CPID) with the differences highlighted;

- Updated product monograph (annotated/tracked and non-annotated) with date of revision; and

- Justification why a bioavailability study is not required, or

- Evidence of interchangeability of the old and new formulations (e.g. clinical/bioequivalence study, pharmaceutical equivalence study etc.) as applicable.
e. Change in the Approved Drug Indication

1. For Products listed as Limited Use (LU) in the Formulary

A full new submission is required for new indication approved by Health Canada for all products listed as non-General Benefit (i.e. LU) products in the Formulary.

2. For Product listed as General Benefit (GB) in the Formulary

If Health Canada has approved the change, the manufacturer should submit documentation [e.g., No Objection Letter (NOL)] demonstrating that the bioavailability of the drug product was not affected:

- Signed & dated covering letter on company letterhead that includes:
  a) The type of notification (i.e. level of change);
  b) Narrative of the change(s);
  c) A brief rationale for the change(s);
  d) Listing of all drug products, including the DIN(s), which are affected by the
  e) Confirmation that the master formulation has not changed; and
  f) Confirmation that the bioavailability has not been affected.

- Evidence that Health Canada has approved the change:
  a) Notice of Compliance (NOC) and/or No Objection Letter (NOL) and;
     i. Where No Objection Letter is not available, linkage information such as email correspondence with Health Canada;
  b) Completed Drug Notification Form (DNF) dated and signed (if applicable);
  c) A copy of most recent change in the Drug Product Database.
 Updated product monograph (annotated/tracked and non-annotated) with the date of revision;

 Old and new master formulation with the differences highlighted, if applicable; and

 Additional linkage information that Health Canada has approved the change.

**Please note**: The ministry reserves the right to require a full new submission on the new indication.

For type of changes not listed above, please contact the ministry for the requirements on the changes.
PART IV

GUIDELINES FOR DIABETIC TESTING AGENTS
For the purpose of this document, the ministry interprets “listed substance” to mean a product, other than a drug, that is approved and reimbursed by the Executive Officer to ODB eligible recipients. This includes but is not limited to diabetic testing agents, natural health products, and nutrition products. As a result, a submission for these products will undergo a similar review process as a drug product.

A submission for a diabetic testing agent [i.e., blood glucose test strip (BGTS)] undergoes a similar review process as a drug product, although the manufacturer must satisfy a different set of requirements to be considered for reimbursement on the Formulary.

A Committee to Evaluate Drugs (CED) consultant first reviews the submission. As with drug products, the CED as a whole is asked to make a final recommendation to the Executive Officer regarding the reimbursement of diabetic testing agents.

**BGTS Reimbursement**

Effective December 1, 2015, the ministry has implemented a new pricing model for Blood Glucose Testing Strip (BGTS). The new BGTS pricing model replaces the Maximum Allowable Reimbursement (MAR) Schedule with a Pricing Schedule. In this new Pricing Schedule, the “Amount Patient Pays” portion has been eliminated from the payment scheme. Pharmacies cannot charge eligible ODB recipients any amount other than the co-payment for supplying BGTS under the ODB Program.

Removing the “Amount Patient Pays” portion will increase coverage for ODB recipients while maintaining access to currently listed BGTS. The ministry will reimburse pharmacies the amount identified in the column Amount MOHLTC Pays.

As before, pharmacies will not be entitled to a mark-up for supplying BGTS. In addition, Cost-to-Operator claims will not be accepted.

Because of these rules, manufacturers of BGTS listed on the Formulary can only sell their BGTS to pharmacy operators at the “Amount MOHLTC Pays” price. Any mark-ups that would normally be charged by the manufacturer or wholesaler on the BGTS must be built-into the “pharmacy acquisition price” that is submitted to the ministry (see submission requirements below).
Reimbursement Limits for Eligible Persons

There will be no changes to the BGTS reimbursement limits which became effective on August 1, 2013. The Health Network System (HNS) will continue to track and determine the appropriate levels of reimbursement of BGTS based on the current diabetes therapy used by eligible ODB recipients.

| Submission Requirements |

A manufacturer may satisfy the submission requirements by submitting one hard copy and one electronic copy (CDs, DVDs or USB keys) of the following:

(a) Cover Letter
   
   The letter should include a subject heading that adheres to the following format:
   
   Re: <insert product name/generic name, strength, dosage form and package format and size> (the “Product”) manufactured by <insert name of manufacturer> (“the Manufacturer”), and ministry assigned Master File No. and Product File No., if applicable.

(b) Evidence that Health Canada has issued an authorization (i.e. Medical Device Licence and Medical Device Establishment Licence, as applicable) for the sale or importation of a diabetic testing agent in Canada;

(c) A letter authorizing the Minister to gain access to all information with respect to the product in the possession of Health Canada or of the government of any province or territory in Canada and authorizing the Minister to disclose any information with respect to the product in the possession of the ministry to Health Canada or of the government of any province or territory in Canada (refer to Part VII of the Guidelines for the template letter);

(d) Clearly indicate the following two prices:
   
   (1) Manufacturer list price (price without mark-up): the lowest price per package size and per strip to four decimal places sold to wholesalers or pharmacies (if direct distribution to pharmacies).

   (2) Pharmacy acquisition price (price with mark-up): the lowest price per package size and per strip to four decimal places that includes the mark-up (intended to cover any distribution costs charged by the wholesaler to the pharmacies). Indicate the mark-up amount in both dollars and
percentage.

In cases where the cost per strip is different from the cost per pack divided by the number of strips in each package, the lowest price will be used.

(e) A letter dated and signed by a senior company official confirming the ability to supply product at the submitted price for distribution in a quantity sufficient to meet the anticipated demand. Refer to Part VII of the Guidelines for the template letter;

(f) Evidence of the product's effectiveness including precision, linearity, bias, interference, accuracy, variability and reliability over an appropriate range of values, as well as clinical testing in patients;

(g) Specifications for the finished product;

(h) A copy of instructions (patient package insert, prescriber information/insert for the therapeutic use of the product);

(i) A sample of the label of the finished product as it is intended to be sold in Canada;

(j) ODB market share penetration or impact analysis on ODB expenditure, including the underlying assumptions for the calculations; and

(k) Certification that no rebates were provided to a person listed under section 11.5(1) of the ODBA since Health Canada approved the product for sale in Canada. Refer to Part VII of the Guidelines for the template letter.

The submission will be deemed incomplete if any of the above components are missing.
Establishment License

No manufacturer shall import or sell a blood glucose monitoring in vitro diagnostic device unless Health Canada has issued an authorization for its sale or importation. These medical devices must meet the safety and effectiveness requirements established by Health Canada.

Evidence of Safety and Effectiveness of Product

Submissions should include the following data to support the product’s precision, accuracy, variability and reliability:

- Within day performance
- Between day performance
- Environmental testing: effect of varying temperature (minimum of 1 low temperature (5°-10° C), room temp (20° -25° C) and 1 elevated temperature (35-45C). At least 3 glucose concentrations covering the range of the test strip should be tested at each temperature.
- Environmental testing: effect of varying humidity (minimum of 1 low humidity (~10%), 1 mid-range humidity (35-65%) and 1 high humidity (>85%). At least 3 glucose concentrations covering the range of the test strip should be tested at each humidity.
- Dynamic range for glucose
- Comparison of accuracy against a standard YSI glucose analyzer
- Sensor movement testing
- Sample volume (accuracy of glucose concentrations with varying sample volumes)
- Oxygen sensitivity testing (testing at a partial pressure of oxygen equivalent to sea level and 10,000 ft or higher).
- Interference testing with a battery of at least 15 chemicals which could potentially interfere on the basis of strip chemistry and monitor technology.
- Stability
- Hematocrit testing (minimum of 5 hematocrits tested from a low of at least 20% to a high of 60% or greater). At least 3 glucose concentrations covering the range of the test strip should be tested at each hematocrit.
Human Factor Study and Consumer Study Field Testing

**Guidance on Studies and standards is provided at the end of this section.**

**Note:** Where applicable, raw data and a quantification of deviations between individual samples should be provided.

If certain information or data are not provided in the submission, an adequate justification must be given by the manufacturer or the submission will be deemed incomplete and will not proceed further in the review process.

**Format and Organization of Submissions**

The manufacturer must submit one hard copy and one electronic copy (CDs, DVDs or USB keys) for each submission, and any material responding to any deficiency from the Ministry’s Notice of Drug Submission Status (NDSS) or CED recommendation letters.

The electronic copy:

- The documents must be provided in MS Word or PDF format that is unlocked, searchable and printable.
- Users must have the ability to extract information or combine documents.
- For the economic information, a model e.g. spreadsheet that is unlocked (or executable) must be provided. The user should be able to specify inputs, view calculations, and run various analyses.

**Notification of Change**

The ministry must be notified of changes to the license, ownership of the product, changes to the product monograph and master formulation where the changes are may affect the quality or performance of the product. The manufacturer must provide evidence to support the change.
**Guidance on Studies and Standards**

Please note that this guidance document is meant to provide assistance to manufacturers on how to conduct the study.

It is important to note that the ministry reserves the right to request additional information or material, or defined conditions not specifically described in the Guidelines, in order to allow the Committee to Evaluate Drugs and / or the ministry to adequately assess the safety, efficacy or quality of the product.

**Evidence of safety and effectiveness of product**

Submissions should include the following data to support the product’s precision, accuracy, variability and reliability. Data should be appropriately summarized, but where accuracy is being evaluated, deviations should be based on results of a standard analyser (YSI instrument or equivalent) and reporting only the mean deviation is not appropriate or sufficient. In general, results will be judged as acceptable for a particular test, only if 95% of all individual test strip results, relative to a standard glucose analyser, fall within Zone A on an error grid and 98% fall into Zones A plus B.

1. **Within day performance**
   a. Submitted data must span the entire operating range of the test strip and meter. It is suggested that an upper value equivalent to 90% of the upper limit of the operating range is appropriate. Results will be judged as acceptable only if 95% of all individual test strip results fall within Zone A on an error grid and 98% fall into Zones A plus B.

2. **Between day performance**
   a. Submitted data must span the entire operating range of the test strip and meter. It is suggested that an upper value equivalent to 90% of the upper limit of the operating range is appropriate. Results will be judged as acceptable only if 95% of all individual test strip results fall within Zone A on an error grid and 98% fall into Zones A plus B.
3. Environmental testing: effect of varying temperature (minimum of one low temperature (5°-10°C), room temp (20°-25°C) and one elevated temperature (35°-45°C).

   a. Test meters and test strips must not be allowed to re-equilibrate to room temperature or standard humidity (~50%) prior to testing. At each temperature a variety of glucose concentrations should be tested (a minimum of two glucose concentrations less than 4.2 mmol/L (75 mg/dL) and a minimum of three glucose concentrations above 4.2 mmol/L (75 mg/dL)). The range of concentrations selected should evaluate the operating range of the test strip. It is suggested that an upper value equivalent to 90% of the upper limit of the operating range is appropriate.

   b. Individual deviations must be determined based on a standard glucose analyzer (YSI) result. Deviations should be segregated by environment temperature and/or humidity.

   c. Results should be presented at each environmental condition. Results at one concentration should not be pooled across environmental conditions. Furthermore, it is preferable that data be presented in an error grid although a deviation plot is acceptable.

   d. Results will be judged as acceptable only if, in the combined pool of high and low concentrations, 95% fall within Zone A on an error grid and 98% fall into Zones A plus B, for each temperature.

4. Environmental testing: effect of varying humidity (minimum of one low humidity (10%), one mid-range humidity (25% - 75%) and one high humidity (90%).

   a. Test meters and test strips must not be allowed to re-equilibrate to room temperature or standard humidity (~50%) prior to testing. At each humidity level a variety of glucose concentrations should be tested (two glucose concentrations less than 4.2 mmol/L (75 mg/dL) and three or four above 4.2 mmol/L (75 mg/dL)). The range of concentrations selected should evaluate the operating range of the test strip. It is suggested that an upper value equivalent to 90% of the upper limit of the operating range is appropriate.

   b. Individual deviations must be determined based on a standard glucose analyzer (YSI) result. Deviations should be segregated by environment temperature and/or humidity.
c. Results should be presented at each environmental condition. Results at one concentration should not be pooled across environmental conditions. Furthermore, it is preferable that data be presented in an error grid although a deviation plot is acceptable.

d. Results will be judged as acceptable only if, in the combined pool of high and low concentrations, 95% fall within Zone A on an error grid and 98% fall into Zones A plus B, for each humidity level.

5. Oxygen sensitivity testing (testing at a partial pressure of oxygen equivalent to sea level and 10,000 ft or higher).

a. Test conditions at sea level and 10,000 ft represent the minimum required test conditions. At each altitude a variety of glucose concentrations should be tested (two glucose concentrations less than 4.2 mmol/L (75 mg/dL) and three or four above 4.2 mmol/L (75 mg/dL)). The range of concentrations selected should evaluate the operating range of the test strip. It is suggested that an upper value equivalent to 90% of the upper limit of the operating range is appropriate.

b. Individual deviations must be determined based on a standard glucose analyzer (YSI) result. Deviations should be segregated by altitude.

c. Results should be presented at each altitude. Results at one concentration should not be pooled across altitudes. Furthermore, it is preferable that data be presented in an error grid although a deviation plot is acceptable.

d. Results will be judged as acceptable only if, in the combined pool of high and low concentrations, 95% fall within Zone A on an error grid and 98% fall into Zones A plus B, for each altitude.

6. Comparison of accuracy against a standard glucose analyzer (YSI).

a. At least 200 reagent system units, from at least 10 vials or packages, shall be used.

b. The ISO guideline for clinical accuracy (ISO 15197) must be followed. Samples will be drawn from patients and must fill the concentration bands specified in the table below until the band is filled. Once a concentration category is filled, no more samples shall be added to that category. Samples in lowest and highest bands may require glycolysis or spiking to achieve the proper number of samples in the concentration band:
Glucose concentrations of samples for system accuracy evaluation

<table>
<thead>
<tr>
<th>Required Percentage of Samples in Specified Concentration Range</th>
<th>Glucose concentration mmol/L (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>&lt; 2.8 (&lt; 50)</td>
</tr>
<tr>
<td>15</td>
<td>2.8 to 4.3 (50 to 80)</td>
</tr>
<tr>
<td>20</td>
<td>4.4 to 6.7 (80 to 120)</td>
</tr>
<tr>
<td>30</td>
<td>6.7 to 11.1 (120 to 200)</td>
</tr>
<tr>
<td>15</td>
<td>11.2 to 16.6 (201 to 300)</td>
</tr>
<tr>
<td>10</td>
<td>16.7 to 22.2 (301 to 400)</td>
</tr>
<tr>
<td>5</td>
<td>&gt; 22.2 (&gt; 400)</td>
</tr>
</tbody>
</table>

c. Results may be presented in a variety of formats, including tabulation of proportion of samples deviating from the standard glucose analyzer (YSI) concentration, using deviation plots, or an error grid plot.

d. Results will be judged as acceptable only if, in the combined pool of high and low concentrations, 95% fall within Zone A on an error grid and 98% fall into Zones A plus B.

7. Interference testing with at least 15 chemicals which could potentially interfere on the basis of strip chemistry and monitor technology.

   a. Interference must be reported for a minimum of 15 chemicals at both high (>4.2 mmol/L or 75 mg/dL) and low (<4.2 mmol/L or 75 mg/dL) glucose concentrations.

   b. Submissions should include tests for compounds which test the specificity of the test strip and its accuracy with high, clinically achievable concentrations for each interfering compound.

   c. Where interference is clearly minor (e.g. observed bias or shift in glucose concentration determined by a standard analyzer (YSI) is less than 10% at all concentrations) tabulation is sufficient.

   d. When interference from a compound at a clinically achievable concentration is observed to be more than 10%, evidence demonstrating that the compound does not cause clinically important deviations should be provided.
e. Results will be deemed as not causing a clinically important interference only if, in the combined pool of high and low concentrations, 95% fall within Zone A on an error grid and 98% fall into Zones A plus B.

8. Hematocrit testing (minimum of five hematocrit levels tested from a low of at least 20% to a high of 60% or greater).

a. Test conditions must include a hematocrit of less than 30%, however, a hematocrit of 20% is preferred. Submissions where the lowest test hematocrit is greater than 20% will be required to provide justification for the lowest tested hematocrit level. A product monograph statement cautioning of inaccuracies below hematocrit levels of 30% is not sufficient justification.

b. At each hematocrit level a variety of glucose concentrations should be tested (two glucose concentrations less than 4.2 mmol/L (75 mg/dL) and three or four above 4.2 mmol/L (75 mg/dL)). The range of concentrations selected should evaluate the operating range of the test strip. It is suggested that an upper value equivalent to 90% of the upper limit of the operating range is appropriate.

c. Individual deviations must be determined based on a standard glucose analyzer (YSI) result. Deviations should be segregated by hematocrit levels.

d. Results should be presented at each hematocrit level. Results at one concentration should not be pooled across hematocrit levels. Furthermore, it is preferable that data be presented in an error grid although a deviation plot is acceptable.

e. Results will be judged as acceptable only if, in the combined pool of high and low concentrations, 95% fall within Zone A on an error grid and 98% fall into Zones A plus B for each evaluated hematocrit level.

9. Human Factor Study and Consumer Study Field Testing

a. Submissions should follow the ISO protocol and at least 50 subjects are to be included for each lot tested.

b. Results will be judged as acceptable only if, in the combined pool of high and low concentrations, 95% fall within Zone A on an error grid and 98% fall into Zones A plus B.
10. Sample volume (accuracy of glucose concentrations with varying sample volumes)

a. Submissions should follow the ISO protocol and demonstrate that, at the product monograph stated minimum volume, a sample result is produced and is accurate across the operating range of the test strip and meter. Minimally this must include one concentration less than 4.2 mmol/L (75 mg/dL), a mid-range glucose concentration above 4.2 mmol/L (75 mg/dL) and a third concentration near the upper limit of the operating range of the meter and test strip.

b. Individual deviations should be determined based on a standard glucose analyzer (YSI) result.

c. Results should be presented for each volume tested. It is preferable that data be presented in an error grid although a deviation plot is acceptable.

d. Results will be judged as acceptable only if, in the combined pool of high and low concentrations, 95% fall within Zone A on an error grid and 98% fall into Zones A plus B, for each evaluated sample volume.

11. Dynamic Range, Linearity for glucose

a. Submissions should follow the Clinical and Laboratory Standards Institute (CLSI) guidance document, entitled: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline, or other equivalent evaluation/guideline. The reportable range of the system may be established by demonstrating linearity of known glucose concentrations relative to a standard glucose analyzer’s (YSI) reported glucose concentrations.

b. Test concentrations should cover the operating range of the meter and test strip.

c. Individual deviations should be determined based on a standard glucose analyzer (YSI) result.

d. Regression statistics should be presented and should evaluate slope, and intercept as well as the change in deviation with concentration based on a standard glucose analyzer’s (YSI) result.
Each submission should also include other tests noted below. These tests are included in the Health Canada Device review and the ministry will accept these results:

- Stability
- Sensor movement testing

**Note:** Where applicable, raw data and a quantification of deviations between individual samples should be provided. Reporting only the mean deviation is not acceptable.
PART V

MAXIMUM ALLOWABLE AND REIMBURSEMENT (MAR) SCHEDULE

SUBMISSION GUIDELINES FOR NUTRITION PRODUCTS
For the purpose of this document, the ministry interprets “listed substance” to mean a product, other than a drug, that is approved and reimbursed by the Executive Officer to ODB eligible recipients. This includes but is not limited to diabetic testing agents, natural health products, and nutrition products. As a result, a submission for these products will undergo a similar review process as a drug product.

Nutrition products are considered to be “listed substances” for the purpose of the ODBA.

Although a submission for a nutrition product undergoes a similar review process as a drug product, the manufacturer must satisfy a different set of requirements to be considered for reimbursement according to the Maximum Allowable Reimbursement (MAR) mechanism and pricing schedule. In the case of nutrition products, a CED nutrition consultant first reviews the complete submission. As with drug products, the CED is asked to make a final recommendation to the ministry regarding the reimbursement of nutrition products. Please refer to the Formulary for more information on MAR and to Part II: Detailed Submission Requirements for Formulary Listing Process for more detail on the review process.

Please note that a nutrition product will not be reimbursed under the ODB program if:

- The product is advertised in Ontario to the public; or
- The distributor is not located in Canada and relies on a direct sales network; or
- The product is intended for any of the following uses:
  - prescribed weight loss in the treatment of obesity
  - food allergies
  - body building
  - voluntary meal replacement
  - nutritional supplement
  - convenience
  - use as a replacement for breast feeding for infants with normal gastrointestinal absorptive function.
Submission Requirements

Manufacturers must provide the following information:

- **Cover Letter**
  
  The letter should include a subject heading that adheres to the following format:

  Re:  <insert product name/generic name, strength, dosage form, package format and size > (the “Product”) manufactured by <insert name of manufacturer> (“the Manufacturer”), and ministry assigned Master File No and Product File No., if applicable;

- **Confirmation for the submitted product that:**
  
  o the product is not advertised in Ontario to the public; or
  o the distributor is located in Canada and does not relies on a direct sales network; or
  o the product is not intended for any of the following uses:
    - prescribed weight loss in the treatment of obesity
    - food allergies
    - body building
    - voluntary meal replacement
    - nutritional supplement
    - convenience
    - use as a replacement for breast feeding for infants with normal gastrointestinal absorptive function.

- A completed Nutrition Product Summary Sheet;

- A completed Nutrition Product Work Sheet
  
  o The Nutrition Product Worksheet was developed based on the guidelines that CED reviewers use during their evaluation. It was designed to help manufacturers prepare submissions that are easy to review and ensure submissions proactively address the CED’s usual questions;
• Documentation with respect to complete ingredients, nutrient analysis of the product and the quantitative formula, including support for the classification of the nutrition product (e.g., polymeric, semi-elemental or elemental, or modular product);

• Daily volume to meet Recommended Nutrient Intake (RNI);

• A sample of the finished label of the product as it is intended to be sold in Canada;

• Clearly indicate the following two prices:

  1. Manufacturer list price (price without mark-up): the lowest price per unit (mL, g) and per package size to four decimal places sold to wholesalers or pharmacies (if direct distribution to pharmacies).

  2. Pharmacy acquisition price (price with mark-up): the lowest price per unit (mL, g), per package size and per 1000 kcal, to four decimal places that include the mark-up (intended to cover any distribution costs charged by the wholesaler to the pharmacies). Indicate the mark-up amount in both dollars and percentage. Also indicate the amount of calories in kcal per unit (mL, g) and per package size of each product.

Note that the maximum allowable mark-up for nutrition products is identical to that prescribed for purposes of paragraph 3 of subsection 6(1) of the Ontario Drug Benefit Act. Refer to Part II of the ODB Formulary for more information.

Where patients are required to make a co-payment (i.e., the submitted price with mark-up is above the current MAR limit), please provide the amount that patients are required to pay to four decimal places and a justification for this incremental cost.

• Documentation with respect to the indications of use;

• Product specific clinical studies (published or unpublished) mandatory; and other clinical evidence of the product’s therapeutic effectiveness or efficacy and of the product’s safety, including any information that relates to adverse reactions.
Comparative studies evaluating the product’s therapeutic effectiveness or efficacy and the product’s safety to that of other products or treatments is of particular interest.

- Clinical study on each pack size is not required if they are of the same container system (open-open or closed-closed system), however, similar stability must be demonstrated at the recommended storage conditions on all sizes (refer to changes section);

- Evidence demonstrating the benefit of the product in relation to the cost of the product and to any alternative products or treatments, if available.

- Certification that no rebates were provided to a person listed in subsection 11.5(1) of the ODBA since Health Canada approved the product for sale in Canada. Refer to Part VII of the Guidelines for the template letter.

Submissions that do not contain the required information will be deemed incomplete and will not proceed further in the review process.

**Note that the maximum allowable mark-up for nutritional products is identical to that prescribed for the purposes of paragraph 3 of subsection 6(1) of the Ontario Drug Benefit Act. Refer to Part II of the Formulary for more information.**

A manufacturer must inform the ministry of all formulation changes, changes in classification under the Food and Drug Act, changes in the ownership of the manufacturer, changes in product name, change in package size and changes in advertising policy. The following information must be submitted to support these changes:

**Change in Ownership**

- Detailed explanation of the change;

- Business agreement letter between companies;

- Provide confirmation that the change will not impact clinical response or product safety; and

- A copy of the product label for sale in the Canadian market.
**Change in Product Name**
- Detailed explanation of the change;
- Provide confirmation that the change will not impact clinical response or product safety; and
- A copy of the product label for sale in the Canadian market.

**Change in Existing Listed Package Size**
- Detailed explanation of the change;
- Justification of the new pack size;
- Indicate if the change will impact clinical response or product safety. If it will impact clinical response or product safety, include the supporting information/or/study listed for the Nutrition Product Work Sheet;
- Comparative stability study test data for the listed and the new pack size(s) are required for review. The study test data must demonstrate that all new pack size(s) are comparable in terms of performance and product quality to support the product shelf life;
- A copy of the stability study protocol/design for all pack sizes must be provided;
- A copy of the product label for sale in the Canadian market; and
- A new Nutrition Product Work sheet and the supporting information or study listed in the Work Sheet.

**Line Extension of Existing Package format**
Manufacturers may request listing for additional package formats for a listed nutrition product. The following information is required:

- Detailed explanation of the change;
- Justification of the new package format;
- Indicate if the change will impact clinical response or product safety. If it will impact clinical response or product safety, include the supporting information or study listed for the Nutrition Product Work Sheet;
- Comparative stability study test data for both old and new formats are required for review. The study test data must demonstrate that old and new package formats are
comparable in terms of performance and product quality to support the product shelf life.

- A copy of the stability study protocol/design for old and new formats must be provided;
- A copy of the product label for sale in the Canadian market; and
- A new Nutrition Product Work sheet and the supporting information or study listed in the Work Sheet.

**Change in Formulation**

The manufacturer must submit:

- Detailed explanation of the change;
- Rationale for the change(s);
- Old and new quantitative formula and nutrient formulation with the differences highlighted;
- A copy of the product label;
- Evidence that changes are not significant enough to alter product efficacy, tolerance and/or safety; and
- A new Nutrition Product Work sheet and the supporting information or study listed in the Work Sheet.

The ministry may require **product specific** clinical studies for the new formulation if the manufactures have not provided satisfactory evidence to demonstrate that the product efficacy, tolerance and/or safety are not altered.

**Format and Organization of Submissions**

The manufacturer must submit one hard copy and one electronic copy (CDs, DVDs or USB keys) for each submission, and any material responding to any deficiency from the ministry’s NDSS or CED recommendation letters.

For the electronic copy:

- The documents must be provided in MS Word or PDF format that is unlocked, searchable and printable.
- Users must have the ability to extract information or combine documents.
Guidance on Clinical Study

Please note that the suggested clinical requirements are meant to provide assistance to manufacturers on how to conduct the study. This may include, but not limited to, the following “Suggested on Clinical Study Requirements”.

It is important to note that the ministry reserves the right to request additional information or material, or defined conditions not specifically described in the Guidelines, in order to allow the Committee to Evaluate Drugs and / or the ministry to adequately assess the safety, efficacy or quality of the product.

Suggested on Clinical Study Requirements

1. The studies do not need to be Canadian but must be generalizable to the Canadian population.

2. Studies do not need to be published. Data on file is sufficient but must be presented in sufficient detail for a reviewer to determine the validity of the study.

3. Clinical trial should be conducted with patients who need the product.
   a. The trial can be open label.
   b. At least 25 subjects would need to be included, but depending on the difference expected, the number of subjects required can be calculated.
   c. Patient selection is important.
      i. Researcher should decide the inclusion/exclusion criteria well before admitting patients to the study, taking into account:
         1. patients for which the product is indicated.
         2. similarities amongst patients with respect to disease states and confounding factors
      ii. Reasonable chance of survival for the study and disease states that would allow the effect of nutrition to be assessed.
      iii. The selection of patients, the endpoint measures etc should be justified in the report. For example if an endpoint measuring nutritional status is chosen the report should indicate why it is an appropriate measure especially if the measure is not routinely used in the field.
d. Dose should be standardized to body mass index (BMI), or similar indices (e.g. ideal BMI, target BMI).
e. Duration of treatment (2 to 3 weeks) should be sufficient to be able to observe an effect of the nutrition.
f. The outcome of the study may vary. Usually the efficacy parameter measured should be a change in BMI or maintenance of BMI. The study could also measure surrogate markers of changes in nutritional status (e.g. Albumin). The efficacy measure should be justified especially if it is not routinely used in the field.
g. Comparator used should be the standard of care, that is, the comparator should be another nutritional product that has been shown to be effective. Historical controls can be considered but must be justified. Preference should be given to an active control that is established. Use of a control will increase the number of subjects needed.
h. Compare the new product to the accepted product in patients who need nutrition from this type of products and the endpoint expected would be that the new product is equally effective to the old product.
i. Adverse events—tolerability should be measured as well.

4. The formulation composition of the test products.
# NUTRITION PRODUCT SUMMARY SHEET

Date____________________

## Product Information

<table>
<thead>
<tr>
<th>Product Name/Strength/dosage Form</th>
<th>Name &amp; Address of Manufacturer and/or Canadian distributor</th>
</tr>
</thead>
</table>

1. Submission
   - New Product
   - Notice of Change

2. Does this product comply with Food and Drug Regulations? Yes ☐ No ☐

3. Have you indicated the product’s classification under the Food and Drug Regulations? Yes ☐ No ☐

4. Have you indicated the category in the Ontario Drug Benefit Formulary/Comparative Drug Index sought? Yes ☐ No ☐

5. Is this product advertised or planned to be advertised to the public in Ontario? Yes ☐ No ☐

6. Have you summarized submitted clinical documentation in the specified table? Yes ☐ No ☐

7. Have you completed the nutrient analysis table? Yes ☐ No ☐
8. Have you submitted the required pricing information?  

Yes ☐  No ☐

9. Administrative Issues

- Are two complete sets of the submission provided?  
  Yes ☐  No ☐

- Is the submission well organised, tabbed and indexed according to the relevant section of the requirements?  
  Yes ☐  No ☐

- Is a table of contents included in the submission?  
  Yes ☐  No ☐
**NUTRITION PRODUCT WORK SHEET**

Date__________________

<table>
<thead>
<tr>
<th>Product Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Name/Strength/Dosage Form</td>
</tr>
<tr>
<td>Name &amp; Address of Manufacturer and/or Canadian distributor</td>
</tr>
</tbody>
</table>

Please answer the following questions and complete the table below.

1. How is the product classified under the federal *Food and Drug Regulations*?  
   - Formulated liquid diet  
   - Meal replacement  
   - Human milk substitute/infant formula  
   - Unstandardized food  
   - Other  
   - Specify__________________________

2. Under which Nutrition Product category in the Ontario Drug Benefit Formulary should the product be considered for listing?  
   - A. Complete Polymeric  
     - (1) Lactose Free  
     - (2) Lactose Containing  
     - (3) Fibre Containing  
     - (4) High Nitrogen  
   - B. Incomplete Polymeric  
   - C. Modular  
     - (1) Protein
3. Is the product advertised to the Ontario public now or will it be advertised to the Ontario public in the future? Yes ☐ No ☐

4. Is the product suitable for sole source nutrition? Yes ☐ No ☐

5. List the indications for the product and provide rationale for the indications.

6. Please submit relevant documentation organized in a binder as follows:

1. Summary of the relevance of each document supporting this product.

2. Clinical studies (published and unpublished studies that address the key clinical issue for the submitted product);

3. Other studies and supporting documents (e.g. abstracts, consensus statements, review articles).

4. Summary of the submitted documentation in a table as follows.
<table>
<thead>
<tr>
<th># Published clinical trials</th>
<th>With product specific nutrition product</th>
<th>With comparable nutrition product</th>
</tr>
</thead>
<tbody>
<tr>
<td># Published case series/studies</td>
<td>With product specific nutrition product</td>
<td>With comparable nutrition product</td>
</tr>
<tr>
<td># Published abstracts</td>
<td>With product specific nutrition product</td>
<td>With comparable nutrition product</td>
</tr>
<tr>
<td># Supporting literature (secondary research, bibliography etc.)</td>
<td>Related to nutrition product</td>
<td>Unrelated/ general nutrition</td>
</tr>
<tr>
<td># Anecdotal information/internal unpublished documentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td># Clinical trials conducted with appropriate target population</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7. Product description:

Product form:  Liquid – Can  
Liquid – Ready-to-hang  
Powder  
Other
<table>
<thead>
<tr>
<th>Descriptive Item</th>
<th>Product Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Package size (g or mL)</td>
<td></td>
</tr>
<tr>
<td>Total Kcal per package (g or mL)</td>
<td></td>
</tr>
<tr>
<td>Kcal per g</td>
<td></td>
</tr>
<tr>
<td>Kcal per mL**</td>
<td></td>
</tr>
</tbody>
</table>

Additional columns can be added if there is more than one dosage form (e.g., liquid, powder) or more than one package size of the product.

** If applicable, please include the conversion factor from g to mL by clearly indicating the quantity of weight (in grams) to the final volume.
8. **Nutrient analysis: Nutrient Analysis Table**

A. Complete column as indicated

<table>
<thead>
<tr>
<th>Protein Source</th>
<th>Recommended volume intake for target population (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat Source</td>
<td>Amount in recommended volume</td>
</tr>
<tr>
<td>Carbohydrate Source</td>
<td>Carbohydrate g</td>
</tr>
<tr>
<td>Fibre Source (if applicable)</td>
<td>Dietary Fibre g</td>
</tr>
<tr>
<td>Calorie:nitrogen ratio</td>
<td>Total Fat g</td>
</tr>
<tr>
<td>Non-protein Calorie:nitrogen ratio</td>
<td>Cholesterol g</td>
</tr>
<tr>
<td>Osmolality (mOsm/ kg water)</td>
<td>Polyunsaturated g</td>
</tr>
<tr>
<td>Osmolarity (mOsm/ litre)</td>
<td>Monounsaturated g</td>
</tr>
<tr>
<td>Water (%)</td>
<td>Fatty acids: Linoleic acid g</td>
</tr>
<tr>
<td>Renal Solute load (mOsm/litre)</td>
<td>Linolenic acid g</td>
</tr>
<tr>
<td>Energy density (kJ/mL)</td>
<td>Energy density (kcal/mL)</td>
</tr>
</tbody>
</table>
B. Complete columns as indicated

<table>
<thead>
<tr>
<th></th>
<th>Amount in recommended volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>% total energy</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>% total energy</td>
</tr>
<tr>
<td>Total fat</td>
<td>% total energy</td>
</tr>
<tr>
<td>Saturated Fat</td>
<td>% total energy</td>
</tr>
<tr>
<td>PUFA n-6</td>
<td>% total energy</td>
</tr>
<tr>
<td>PUFA n-3</td>
<td>% total energy</td>
</tr>
<tr>
<td>PUFA n-6/n-3</td>
<td>ratio</td>
</tr>
<tr>
<td>Energy</td>
<td>kJ</td>
</tr>
<tr>
<td></td>
<td>Kcal</td>
</tr>
<tr>
<td>Protein</td>
<td>g</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>RE</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>mcg</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>mg</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>mcg</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>mg</td>
</tr>
<tr>
<td>Thiamine</td>
<td>mg</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>mg</td>
</tr>
<tr>
<td>Niacin</td>
<td>NE</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>mg or mg/g protein</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>mcg</td>
</tr>
<tr>
<td>Folate</td>
<td>mcg</td>
</tr>
<tr>
<td>Nutrient</td>
<td>Amount in recommended volume</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Pantothenic acid</td>
<td>mg</td>
</tr>
<tr>
<td>Biotin</td>
<td>mcg</td>
</tr>
<tr>
<td>Choline</td>
<td>mg</td>
</tr>
<tr>
<td>Calcium</td>
<td>mg</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>mg</td>
</tr>
<tr>
<td>Magnesium</td>
<td>mg</td>
</tr>
<tr>
<td>Iron</td>
<td>mg</td>
</tr>
<tr>
<td>Zinc</td>
<td>mg</td>
</tr>
<tr>
<td>Copper</td>
<td>mg</td>
</tr>
<tr>
<td>Iodine</td>
<td>mcg</td>
</tr>
<tr>
<td>Manganese</td>
<td>mg</td>
</tr>
<tr>
<td>Selenium</td>
<td>mcg</td>
</tr>
<tr>
<td>Chromium</td>
<td>mcg</td>
</tr>
<tr>
<td>Molybdenum</td>
<td>mcg</td>
</tr>
<tr>
<td>Silicon</td>
<td>mcg</td>
</tr>
<tr>
<td>Lithium</td>
<td>mcg</td>
</tr>
<tr>
<td>Boron</td>
<td>mcg</td>
</tr>
<tr>
<td>Nickel</td>
<td>mcg</td>
</tr>
<tr>
<td>Vanadium</td>
<td>mcg</td>
</tr>
<tr>
<td>Arsenic</td>
<td>mcg</td>
</tr>
<tr>
<td>Fluoride</td>
<td>mg</td>
</tr>
<tr>
<td>Sodium</td>
<td>mg</td>
</tr>
<tr>
<td></td>
<td>mmoL</td>
</tr>
<tr>
<td>Potassium</td>
<td>mg</td>
</tr>
<tr>
<td></td>
<td>mmoL</td>
</tr>
<tr>
<td>Chloride</td>
<td>mg</td>
</tr>
<tr>
<td></td>
<td>mmoL</td>
</tr>
</tbody>
</table>
C. Complete amino acid section for nutrition products in Chemically Defined Category, Pediatric Category and nutrition products used for specific disease organ states where amino acid composition is clinically significant,

<table>
<thead>
<tr>
<th>Amino Acids</th>
<th>Amount in recommended volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histidine</td>
<td>mg/g</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>mg/g</td>
</tr>
<tr>
<td>Leucine</td>
<td>mg/g</td>
</tr>
<tr>
<td>Lysine</td>
<td>mg/g</td>
</tr>
<tr>
<td>Methionine + Cystine</td>
<td>mg/g</td>
</tr>
<tr>
<td>Phenylalanine + Tyrosine</td>
<td>mg/g</td>
</tr>
<tr>
<td>Threonine</td>
<td>mg/g</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>mg/g</td>
</tr>
<tr>
<td>Valine</td>
<td>mg/g</td>
</tr>
<tr>
<td>Taurine</td>
<td>mg/g</td>
</tr>
<tr>
<td>Carnitine</td>
<td>mg/g</td>
</tr>
</tbody>
</table>

D. Other Nutrients (as needed)

<table>
<thead>
<tr>
<th>Describe</th>
<th>Specify amount and units in recommended volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
DEFINITIONS OF CATEGORIES OF NUTRITION PRODUCTS

The following definitions for categories of nutrition products in the Formulary are general guidelines for determining the appropriate category for a nutrition product.

A. Complete Polymeric

- These nutrition products are solutions containing macro-nutrients in the form of isolates of intact protein (e.g. calcium and sodium, or calcium and potassium caseinates; soy protein isolates), triglycerides, and carbohydrate polymers, which can be used orally or through a tube, and provide complete nutrition.

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lactose Free</td>
<td>Lactose free</td>
</tr>
<tr>
<td>2. Lactose Containing</td>
<td>Contains lactose</td>
</tr>
<tr>
<td>3. Fibre Containing</td>
<td>Lactose free</td>
</tr>
<tr>
<td></td>
<td>Added fibre or naturally occurring fibre</td>
</tr>
<tr>
<td>4. High Nitrogen</td>
<td>Lactose free</td>
</tr>
<tr>
<td></td>
<td>Protein approximately 18% or greater of total calories</td>
</tr>
</tbody>
</table>

B. Incomplete Polymeric

- These are nutrition products containing macro and/or micronutrients, below Health Canada’s RNI which may be used in conjunction with polymeric products.

C. Modular

- These are single macro-nutrient products that are used in combination with another nutrition product for sole source nutrition or to increase the concentration of the macro-nutrient.

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Protein</td>
<td>Only contains protein</td>
</tr>
<tr>
<td>2. Carbohydrate</td>
<td>Only contains carbohydrate</td>
</tr>
<tr>
<td>3. Fat</td>
<td>Only contains fat</td>
</tr>
</tbody>
</table>
D. Chemically Defined Formula

<table>
<thead>
<tr>
<th>Oligomeric Solutions</th>
<th>Solutions containing peptides and amino acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Other names: Semi-elemental; Chemically Defined)</td>
<td>No lactose or minimal lactose</td>
</tr>
<tr>
<td></td>
<td>No fibre</td>
</tr>
<tr>
<td>Monomeric Solutions</td>
<td>Solutions containing amino acids as the protein source</td>
</tr>
<tr>
<td>(Other names: Elemental; Chemically Defined)</td>
<td>No lactose</td>
</tr>
<tr>
<td></td>
<td>No fibre</td>
</tr>
</tbody>
</table>

E. Pediatric Formula – Complete Polymeric

- These nutrition products are solutions that are specifically adapted to meet the specific nutritional requirements of pediatric patients for growth and development, and considering a variety of disease states. They contain macro-nutrients in the form of isolates of intact protein (e.g. calcium and sodium, or calcium and potassium caseinates; soy protein isolates), triglycerides, and carbohydrate polymers, which can be used orally or through a tube, and provide complete nutrition.

<table>
<thead>
<tr>
<th>1. Lactose Free</th>
<th>Lactose free</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Fibre Containing</td>
<td>Lactose free</td>
</tr>
<tr>
<td></td>
<td>Added fibre or naturally occurring fibre</td>
</tr>
</tbody>
</table>

F. Pediatric Formula – Incomplete Polymeric

- These are nutrition products containing macro and/or micronutrients, below Health Canada’s RNI which may be used in conjunction with polymeric products.
G. Pediatric Formula -- Chemically Defined

<table>
<thead>
<tr>
<th>Oligomeric Solutions</th>
<th>Solutions containing peptides and amino acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Other names: Semi-elemental; Chemically Defined)</td>
<td>No lactose or minimal lactose</td>
</tr>
<tr>
<td></td>
<td>No fibre</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Monomeric Solutions</th>
<th>Solutions containing amino acids as the protein source</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Other names: Elemental; Chemically Defined)</td>
<td>No lactose</td>
</tr>
<tr>
<td></td>
<td>No fibre</td>
</tr>
</tbody>
</table>

H. Pediatric Formula -- Others

- These are nutrition products other than those already described above.
PART VI

OFF-FORMULARY INTERCHANGEABILITY

MULTIPLE SOURCE DRUG PRODUCTS SUBMISSIONS REQUIREMENTS

DRUG INTERCHANGEABILITY AND DISPENSING FEE ACT (DIDFA)

REG. 935
Implementation of Off-Formulary Interchangeability (OFI)

OFI means designating a drug product as interchangeable with an original product but not as a listed drug product (benefit) under the ODB i.e., original product is not listed on the Formulary. The ministry interprets original product to mean a brand name product (typically the innovator product) that has not been listed as a benefit on the Formulary.

For clarity and consistency, “original/innovator” will be used throughout the Guidelines.

A submission for an OFI interchangeable product must meet the regulatory requirements as prescribed in Regulation 935 made under the Drug Interchangeability and Dispensing Fee Act (the “DIDFA Regulation”) and the applicable regulation and policy requirements set out in Part III-B of the Guidelines. A submission must also include all applicable supporting documentation as applicable.

The ministry endeavours to process the OFI submissions two weeks after the cut-off date of new submission deadline (refer to the ministry’s website for the schedule of the new submission deadline). All complete and incomplete Notice of Drug Submission Status (NDSS) letters are usually faxed by 5 p.m. three weeks after the new submission deadline.

If the submission is complete, the manufacturers will only be asked to respond to the Branch if the data (product description, DIN or price, etc.) provided in the letter is incorrect. Any changes/clarification must be provided in writing to the Manager, Benefits Administration one business day from the date of the fax. You may wish to fax your written response; however, the original date document must also be forwarded to the Branch. If there is no response from the manufacturer, the product(s) will go forward for consideration by the EO with no changes. If the manufacturer responds with a correction in one business day timeframe, the ministry will make the appropriate changes so that the product(s) will go forward for consideration by the EO.

In addition to meeting the requirements as set out in Part III-B, the manufacturers must submit the following information in respect of the OFI reference product to facilitate the listing of OFI products.
Reference Product Requirements:

1. Drug Identification Number (DIN);
2. Brand Name;
3. Medicinal Ingredient Name (generic name);
4. Strength;
5. Dosage Form;
6. Original Manufacturer Name; and
7. A copy of summary of bioequivalence study final report between the submitted and reference drug products for oral solid dosage forms, non-aqueous, oil-based solutions, suspension and metered dose inhalers. The study final report must contain the product name, generic name, lot number and expiry date of the submitted and reference products.

When the lot number and expiry date is not found in the protocol, please submit both the bioequivalence study final report and the summary or synopsis of the bioequivalence study so that the required information for item number 7 of the Implementation of Off-Formulary Interchangeability guidance is provided to the ministry.

For aqueous solutions as classified under the Health Canada Guidance for Industry: Pharmaceutical Quality of Aqueous Solutions, the manufacturer must:

- submit a waiver of comparative bioavailability studies for oral solutions, as applicable
- submit a waiver of the requirement to demonstrate in vivo bioequivalence for aqueous solutions,, as applicable;
- provide proof of purchase of Canadian reference product;
- provide a certificate of analysis, i.e., the results of comparative and non-comparative physiochemical parameter tests with the innovator (reference product) demonstrating pharmaceutical equivalence. This includes product name, DIN, strength dosage form and package format (if applicable) and the expiry date of the test and reference products; and
- describe any device attributes, as required by Health Canada.

For pseudogeneric drug product, the manufacturer must provide:
The approved and completed clinical study final report, clinical study summary report or synopsis of the clinical study of the innovator (brand) product. This includes product name, strength dosage form and package format (if applicable) and the expiry date of the brand product.

**Over-the-Counter (OTC) Drug Product or Natural Health Product (NHP)**

The ministry will not accept or consider any submissions for OTC drug products or NHP drug product for considerations of OFI listing.

**Discontinued Reference (Innovator) Product**

The ministry will not consider generic-to-generic comparisons for interchangeability unless the generic reference product is designated and listed as OFI interchangeable with the original/innovator product and the original/innovator product has been discontinued from the Canadian market.

**Policy on Receipt and Format of Submissions**

All submissions and any additional related information must be addressed to:

Senior Manager  
Drug Benefits Management  
Drug Programs Policy and Strategy Branch  
Ontario Public Drug Programs  
Ministry of Health and Long-Term Care  
3rd Floor, 5700 Yonge St.  
Toronto, ON M2M 4K5

The manufacturer must submit one hard copy and one electronic copy (CDs, DVDs or USB keys) for each submission, and any material responding to any deficiency from the ministry’s NDSS or CED recommendation letters.
For the electronic copy:
   o The documents must be provided in MS Word or PDF format that is unlocked, searchable and printable.
   o Users must have the ability to extract information or combine documents.
   o For the Pharmacoeconomic Information, a model (or a spreadsheet) that is unlocked (or executable) must be provided. The user should be able to specify inputs, view calculations, and run various analyses.

Refer to Part II-A.1 for organization of information in submissions.

The ministry will not accept faxed submissions. All submissions must be delivered by either courier services or in person by the manufacturer to the address indicated above by 3:30pm on the scheduled new submission deadline.

All submissions must be organized and indexed. Binders should be sturdy and not overfilled. Manufacturers should restrict individual binders to a maximum of 3 inches in width. Pages must be paginated and double-sided pages are preferred.

To facilitate the review of the clinical/bioequivalence data, as required, the manufacturers should not submit analytical raw data (e.g. laboratory analytical test preparation, LC/GLC chromatograms) for review.

The ministry may return poorly organized OFI submissions to the manufacturer at their expense, without prejudice to refiling.
PART VII

TEMPLATE LETTERS, CHECKLISTS AND WORK SHEETS
1. Template Letters and Forms

**ODBA (Single Source)**

a. Unrestrictive Consent Letter  
b. Product Confirmation Letter  
c. Letter Confirming Ability to Supply  
d. Certification of Providing No Rebate  
e. Letter of Authorization to Collect and Disclose Pre-NOC information  
f. Certification Confirming Product is Not a Private Label Product  
g. Letter on Confirmation of Same Formulation for Clinical and Commercial Lot

**DIDFA (Multi-Source)**

a. Unrestrictive Consent Letter  
b. Product Confirmation Letter  
c. LetterConfirming Ability to Supply  
d. Certification of Providing No Rebate  
e. Letter Confirming No Patent Infringement  
f. Certification Confirming Product is Not a Private Label Product  
g. Letter for Price Exception Rule under Subsection 11(7) of O. Reg. 201/96 of ODBA

2. Checklists and Work Sheets

**ODBA (Single Source)**

a. Submission Summary  
b. Clinical Data Checklist  
c. Pharmacoeconomic Analysis Summary  
d. Pharmacoeconomic Analysis Work Sheet  
e. ODB Financial Impact Analysis Summary Sheet

**DIDFA (Multi-Source)**

a. Submission Summary Sheet DIDFA  
b. Bioequivalence Data Checklist  
c. Pharmacokinetic/Statistical Worksheet
d. Submission Checklist for ODB Multiple Source Drug Products  
e. Aqueous Solution Checklist

**Note:** Manufacturers must not alter the contents of template letter and must ensure that letters are printed on company letterhead. All letters must be dated and signed by an appropriate senior company official.

If a template is altered, the ministry reserves the right to deem the submission incomplete.

Refer to the ministry’s website for current copies of these documents:

Template Letter of Consent

[Manufacturer's letterhead]

[Date]

Director
Drug Programs Policy and Strategy Branch
Ontario Public Drug Programs
Ministry of Health and Long-Term Care
3rd Floor, 5700 Yonge Street
Toronto, ON M2M 4K5

Dear Director:

RE: <insert product name/generic name, strength, and dosage form > (the “Product”) manufactured by <insert name of manufacturer> (“the Manufacturer”)

Pursuant to the requirements under the *Ontario Drug Benefit Act* and *Drug Interchangeability and Dispensing Fee Act* (as applicable) but subject to the limitation concerning confidential pricing information set out below, this letter authorizes Her Majesty the Queen in right of Ontario as represented by the Executive Officer of Ontario Public Drug Programs of the Ministry of Health and Long-Term Care (the “ministry”), both during and after the ministry’s Product evaluation process, to:

(a) collect and use information pertaining to the Product and the Manufacturer in the possession of Health Canada, the government of any province or territory in Canada, the Patented Medicine Prices Review Board, the Canadian Agency for Drugs and Technologies in Health, or Cancer Care Ontario (the “Public Organizations”); and

(b) disclose information pertaining to the Product and the Manufacturer in the possession of the ministry to any of the Public Organizations.

Despite the foregoing, neither the Manufacturer nor the ministry will disclose to any of the Public Organizations any confidential pricing or commercial terms in respect of the Product that are specific to Ontario Public Drug Programs unless the other party has been notified and has authorized the disclosure in writing.

[Signature]

[Name and Title of Senior Company Official]

I have the authority to bind the Manufacturer
[Manufacturer's letterhead]

[Date]

Director
Drug Programs Policy and Strategy Branch
Ontario Public Drug Programs
Ministry of Health and Long-Term Care
3rd Floor, 5700 Yonge Street
Toronto, ON M2M 4K5

Dear Director:

RE: <insert product name/generic name, strength, and dosage form > (the “Product”) manufactured by <insert name of manufacturer> (“the Manufacturer”)

This is to confirm that, except for embossing/markings and labelling, < NOC product name/generic name/strength/dosage form> is identical to the cross-reference product, <product name, manufacturer name> with respect to physical and chemical properties, including strength and dosage form; formulation including both active and inactive ingredients and their quantities; raw materials and finished product specifications; manufacturing process; manufacturing sites; package format and size.

[Signature]

[Name and Title of Senior Company Official]

I have the authority to bind the Manufacturer

Note: There should be two letters of product confirmation submitted (one from NOC holder and one from the Other Party). In instances where the marking of the submitted product is the same as cross-referenced product, the manufacturer must confirm the embossing/marking is the same.
[Manufacturer's letterhead]

[Date]

Director
Drug Programs Policy and Strategy Branch
Ontario Public Drug Programs
Ministry of Health and Long-Term Care
3rd Floor, 5700 Yonge Street
Toronto, ON M2M 4K5

Dear Director:

RE: <<insert Product name/generic name, strength, and dosage form > (the “Product”) manufactured by <insert name of manufacturer> (“the Manufacturer”).

This letter is to confirm that [name of manufacturer] is able to supply the above drug product at the proposed drug benefit price in a quantity sufficient to meet the anticipated demands for this Product.

[Signature]

[Name and Title of Senior Company Official]

I have authority to bind the Manufacturer
[Manufacturer's letterhead]

[Date]

Director
Drug Programs Policy and Strategy Branch
Ontario Public Drug Programs
Ministry of Health and Long-Term Care
3rd Floor, 5700 Yonge Street
Toronto, ON M2M 4K5

Dear Director:

RE: <insert product name/generic name, strength, and dosage form> (the “Product”) manufactured by <insert name of manufacturer> (“the Manufacturer”)

For the purpose of this letter, the following terms have the following meanings:

“DIDFA” means the Drug Interchangeability and Dispensing Fee Act, R.S.O. 1990, c.P.23;

“ODBA” means the Ontario Drug Benefit Act, R.S.O. 1990, c.O.10;

“Person” means one of the persons listed in subsection 12.1(1) of the DIDFA and subsection 11.5(1) of the ODBA;

“Rebate” means a rebate as defined under subsection 12.1(14) of the DIDFA and subsection 11.5(15) of the ODBA.

The Manufacturer hereby represents and warrants that the Manufacturer has not provided a Rebate to any Person with respect to the Product contrary to the ODBA and/or DIDFA since Health Canada approved the Product for sale in Canada.

[Signature]

[Name and Title of Senior Company Official]

I have the authority to bind the Manufacturer.
[Manufacturer's letterhead]

[Date]

Director
Drug Programs Policy and Strategy Branch
Ontario Public Drug Programs
Ministry of Health and Long-Term Care
3rd Floor, 5700 Yonge Street
Toronto, ON  M2M 4K5

Dear Director:

RE: <insert product name/generic name, strength, and dosage form> (the “Product”) manufactured by <insert name of manufacturer> (“the Manufacturer”)

The Manufacturer represents and warrants, to the best of the Manufacturer’s knowledge, that the Product does not infringe any Canadian patents.

The Product is a generic equivalent of <insert name of original/innovator product> manufactured by <insert name of original/innovator manufacturer>.

Summarized below are the number and expiry dates of all Canadian patents, including use patents, for <insert name of original product>:

<table>
<thead>
<tr>
<th>Original/Innovator Product Name</th>
<th>Medicinal Ingredient</th>
<th>Strength</th>
<th>DIN</th>
<th>Patent No.</th>
<th>Date of Expiry</th>
</tr>
</thead>
</table>

*Note: Please provide all strengths for the original/innovator product. Please indicate if the Manufacturer does not market a particular strength for the submitted Product.*

[Signature]

[Name and Title of Senior Company Official]

I have the authority to bind the Manufacturer
Dear Director:

RE: <insert product name/generic name, strength, and dosage form> (the “Product”) manufactured by <insert name of manufacturer> (“the Manufacturer”)

The Manufacturer has made a submission to the Executive Officer to designate the Product as a listed drug product under the Ontario Drug Benefit Act (ODBA) and/or to designate the Product as interchangeable with another product under the Drug Interchangeability and Dispensing Fee Act (DIDFA).

The Manufacturer hereby represents and warrants that the Product is not a private label product, as that term is defined, contrary to the regulations under the ODBA or the DIDFA. The Manufacturer acknowledges that, under those regulations, the term private label product includes a drug product in respect of which,

(a) the manufacturer applying for the designation of the product as a listed drug product does not directly fabricate the product itself, and,
   (i) is not controlled by a person that directly fabricates the product, or
   (ii) does not control the person that directly fabricates the product, and

(b) either,
   (i) the manufacturer does not have an arm’s-length relationship with a wholesaler, an operator of a pharmacy or a company that owns, operates or franchises pharmacies, or
   (ii) the product is to be supplied under a marketing arrangement associating the product with a wholesaler or one or more operators of pharmacies or companies that own, operate or franchise pharmacies.
I acknowledge that under subsection 15(1)(e) of the ODBA it is an offence to knowingly furnish false or incomplete information to the ministry in connection with the administration of the ODBA or the DIDFA.

[Signature]

[Name and Title of Senior Company Official]

I have the authority to bind the Manufacturer
[Manufacturer's letterhead]

[Date]

Director
Drug Programs Policy and Strategy Branch
Ontario Public Drug Programs
Ministry of Health and Long-Term Care
3rd Floor, 5700 Yonge Street
Toronto, ON M2M 4K5

Dear Director:

RE: <insert product name/generic name, strength, and dosage form > (the “Product”) manufactured by <insert name of manufacturer> (“the Manufacturer”)

This letter is to confirm that the Manufacturer is seeking a price exception for its Product that is less than or equal to 50 per cent of the drug benefit price of the original/innovator product pursuant to subsection 11(7) of O. Reg. 201/96 made under the Ontario Drug Benefit Act, and confirms that the Manufacturer meets all of the following terms and conditions:

- The Product was first proposed for designation as a listed drug product on the Ontario Drug Benefit Formulary/Comparative Drug Index (the “Formulary”) on or after April 1, 2012.

- The Manufacturer represents and warrants that the Product proposed for listing has not been previously designated as a listed drug product on the Formulary at any other time.
The Manufacturer represents and warrants that the Manufacturer, or another manufacturer of a product that is interchangeable with the original/innovator product, has successfully challenged the patent(s) of the original/innovator product with the result that the Manufacturer’s Product can be sold in Canada earlier than if the patent(s) had expired or if the challenge had not been brought. In support of this representation and warranty, the Manufacturer submits to the Executive Officer evidence confirming the expiry date of the patent(s) of the original/innovator product and documents, including file numbers or citations of court decision(s), confirming that a court of competent jurisdiction has either:

- dismissed an application brought under subsection 6(1) of the Patented Medicines (Notice of Compliance) Regulations in response to a Notice of Allegation served by the Manufacturer or another manufacturer relating to the patent(s) of the original/innovator product, on one of the following grounds:
  - the allegation that the patent(s) is invalid is justified;
  - the allegation that the statement made under paragraph 4(4)(d) of the Patented Medicines (Notice of Compliance) Regulations is false is justified; or

- pursuant to subsection 60(1) of the Patent Act, declared that the patent(s) of the original product is invalid.

The table attached to this letter as Appendix “A” is a summary of the information that the Manufacturer submits to the Executive Officer for its Product.

The Manufacturer represents and warrants that the Manufacturer has not entered into any arrangement, other than a cross-licensing agreement, with the manufacturer of the original/innovator product with respect to the Product that is proposed for designation as a listed drug product, including any first-to-market arrangement or delayed-entry arrangement.

The Manufacturer agrees and accepts that the exception set out in subsection 11(7) of O. Reg. 201/96 will cease to apply three months (90 calendar days*) after the first product of any manufacturer that is interchangeable with the original/innovator product becomes a listed drug product, at which time the drug benefit price of the Product shall
revert to a price that is less than or equal to 25 per cent (or 35 per cent in the case of a drug product that is not a solid dosage form) of the drug benefit price of the original/innovator product as set out in the Formulary on the date that the Product was first proposed for designation as a listed drug product.

* Note: In cases where the 90th day does not fall on the effective date of an update to the Formulary, the exception will be deemed to no longer apply on the effective date of the Formulary update that immediately follows the end of the 90 days.

[Signature]

[Name and Title of Senior Company Official]

I have the authority to bind the Manufacturer.
## APPENDIX “A”

| Manufacturer: |  |
| Product: |  |
| Date of Notice of Compliance: |  |

<table>
<thead>
<tr>
<th>Original Product Name</th>
<th>Medicinal Ingredient</th>
<th>Strength</th>
<th>Dosage Form</th>
<th>DIN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patent(s) of original/innovator product on Patent Register</th>
<th>Date(s) of Expiry for patent(s) of the original/innovator product</th>
<th>Was a Notice of Allegation served with respect to the patent(s) of the original/innovator product alleging that:</th>
<th>Was an application brought in response to the Notice of Allegation under s.6 (1) of the Patented Medicines (Notice of Compliance) Regulations?</th>
<th>Has a court declared that the patent(s) of the original/innovator product is invalid or void pursuant to s.60 (1) of the Patent Act?</th>
<th>Document(s) to support the dismissal of an application brought under s.6 (1) of the Patented Medicines (Notice of Compliance) Regulations, or a declaration of invalidity under s.60 (1) of the</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>• the patent(s) is not valid, and/or</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>• the statement made in respect of the patent(s)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>If so, was that</td>
<td></td>
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</tbody>
</table>
|                     | under paragraph 4(4)(d) of the *Patented Medicines (Notice of Compliance) Regulations* is false? | application dismissed on the basis that the allegation(s) contained in the Notice of Allegation was justified? | *Patent Act.*
|                     |                                                                                                   |                                                                                                                   | (e.g., the file number or citations of the court decision(s) that order such a dismissal or make such a declaration) |

*Note: Please provide all strengths for the original/innovator product.*
[Manufacturer's letterhead]

[Date]

Director,
Drug Programs Policy and Strategy Branch
Ontario Public Drug Programs
Ministry of Health and Long-Term Care
3rd Floor, 5700 Yonge Street
Toronto, ON M2M 4K5

Dear Director:

RE: Rapid Review of <product name/generic name, strength, and dosage form> (the “Product”) manufactured by <name of manufacturer> (“the Manufacturer”)

BACKGROUND:

- The Manufacturer has made a submission to Health Canada seeking authorization to market and sell the Product in Canada (“Drug Submission”) but has not, as of yet, been issued a Notice of Compliance (“NOC”) in respect of the Product;

- The Manufacturer has also submitted the Product for designation as a listed drug product on the Ontario Formulary under the expedited review process established by s.12(1)(a)(ii) of O. Reg 201/96 made under the Ontario Drug Benefit Act (the “Rapid Review Process”), which permits Her Majesty the Queen in right of Ontario as represented by the Executive Officer for Ontario Public Drug Programs (“Ontario”) to commence review of drug products prior to the issuance by Health Canada of a NOC;

- As a condition of being considered for designation as a listed drug product on the Ontario Formulary through the Rapid Review Process, the Manufacturer must authorize Ontario to obtain information in respect of the Product from Health Canada.
Canada prior to the potential issuance by Health Canada of a NOC for the Product (“Pre-NOC Information”).

For the purposes of this Letter of Authorization, Pre-NOC Information:

(a) includes:

(i) information provided to Health Canada by the Manufacturer as part of the Drug Submission and any other information obtained by Health Canada in connection with the Drug Submission;

(ii) any information, documents or reports, including reviewer reports, created by Health Canada in the course of its review of the Drug Submission; and

(iii) any information pertaining to the Product or the Manufacturer in the possession of the government of any province or territory in Canada, the Patented Medicine Prices Review Board (PMPRB), the Canadian Agency for Drugs and Technologies in Health (CADTH), or Cancer Care Ontario (the “Public Organizations”).

(b) excludes:

(i) third party proprietary information in the possession of Health Canada which Health Canada has agreed with that third party to hold in confidence; and

(ii) any pricing information in respect to the Product which the Manufacturer has supplied to Ontario as confidential information.

AUTHORIZATION OF MANUFACTURER:

The Manufacturer, both during and after the Rapid Review Process, authorizes Ontario to:

(a) collect and use any and all Pre-NOC Information in the possession of Health Canada, the government of any province or territory in Canada, the PMPRB, the CADTH, or Cancer Care Ontario (the “Public Organizations”);

(b) disclose in confidence any and all Pre-NOC Information in the possession of Ontario to Health Canada, the government of a province or territory in Canada, the PMPRB, the CADTH, or Cancer Care Ontario (the “Public Organizations”); and

(c) if the Product is a cancer drug, disclose in confidence any pricing information in respect of the Product to Cancer Care Ontario, or CADTH (the “Public Organizations”).
The Manufacturer further authorizes Health Canada to:

(a) disclose in confidence any and all Pre-NOC Information in its possession to Ontario for use by Ontario, and

(b) respond to any inquiries made by Ontario in respect of Pre-NOC Information disclosed to Ontario pursuant to this Letter of Authorization.

[Signature]

[Name and Title of Senior Company Official]

I have the authority to bind the Manufacturer
Template Letter of
Confirmation of Same Formulation for Clinical and Commercial Lot

[Manufacturer's letterhead]

[Date]

Director
Drug Programs Policy and Strategy Branch
Ontario Public Drug Programs
Ministry of Health and Long-Term Care
3rd Floor, 5700 Yonge Street
Toronto, ON M2M 4K5

Dear Director:

RE: [Product name/generic name, strength, and dosage form (the “Product”) manufactured by <name of manufacturer> (“the Manufacturer”).

This is to confirm that the drug formulation for the clinical test lot(s) <product name, manufacturer name> is identical to the commercial lot(s) of the submitted product, <product name /generic name/strength/dosage form> with respect to physical and chemical properties, including strength and dosage form; formulation, including both active and inactive ingredients and their quantities; raw materials and finished product specifications; manufacturing process; manufacturing sites; package format; and size.

In the case that they are different formulations, please use the following paragraph:

This is to confirm that the drug formulation for the clinical test lot(s) and commercial lot(s) for <insert drug product name> are NOT the same. The differences in formulation are highlighted in the submitted old and new Certified Product Identification Document (CPID). Clinical evidence has been provided to demonstrate that the two formulations are equivalent.

[Signature]

[Name and Title of Senior Company Official]

I have authority to bind the Manufacturer

Ontario Guidelines for Drug Submission and Evaluation
SUBMISSION SUMMARY
For Submissions under ODBA, O. Reg. 201/96

Drug Products (Brand name/generic name/strengths/package format and size):

Submitting Manufacturer:

Please complete all items

Submission Type

1. Submission Type (select on)
   First Review  
   Reconsideration

2. Category/Designation
   a) Submission category (select one)
      New Product
      CDR Product
      New Strength
      New Indication
      New Dosage
      New Format
      Notice of Change
      OTC Drug product
      Natural Health Product
      SDP Drug Product
      Multiple Source (generic) Product
      for Single Source Listing

   b) If applicable, list Formulary designation sought:
      General Benefit
      EAP
      CCO-ODB
      CCO-NDFP
      SDP Program
### 3. Rapid Review Request

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
<th>Page Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Request for a “rapid review” for this submission:</td>
<td></td>
<td></td>
<td>(       )</td>
</tr>
<tr>
<td>b) Justification provided for “rapid review” request:</td>
<td></td>
<td></td>
<td>(       )</td>
</tr>
</tbody>
</table>

### 4. Source and Authorization for Submission

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
<th>Page Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Submitting manufacturer of the submission indicated:</td>
<td></td>
<td></td>
<td>(       )</td>
</tr>
<tr>
<td>b) Is the submitting manufacturer the holder of the Notice of Compliance (NOC)?</td>
<td></td>
<td></td>
<td>(       )</td>
</tr>
</tbody>
</table>

*If not, provide information for 4. (c) and (d)*

**c)** Letter from NOC holder authorizing submitting manufacturer to submit on NOC holder’s behalf: 

**d)** Relationship between each party detailed:  

**e)** Product Confirmation Letter from all parties  

### 5. Administrative Issues

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
<th>Page Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Three complete sets of the submission provided:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) Number of binders that make up each set of a submission:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) Submission is well organized, tabbed and indexed according to the relevant section of the requirements:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d) A table of contents is included in the submission:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 6. Submission Data

**a) Drug Product Dosage Form:**

<table>
<thead>
<tr>
<th>Solid Oral Dosage Form:</th>
<th>Immediate Release</th>
<th>Modified Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solution:</td>
<td>Aqueous</td>
<td>Non-Aqueous</td>
</tr>
<tr>
<td></td>
<td>Cream</td>
<td>Ointment</td>
</tr>
<tr>
<td></td>
<td>Suspension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other: Specify</td>
<td></td>
</tr>
</tbody>
</table>
b) Drug Status:  

<table>
<thead>
<tr>
<th>New Drug</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old Drug</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Drugs that met Health Canada's bioequivalence standards  

Drugs with one or more of the following characteristics (i.e., exceptions that require modifications to Health Canada's standards):

- modified-release dosage forms
- drugs with serious toxicity within the normal dosage range
- drugs exhibiting non-linear pharmacokinetics
- drugs with a terminal elimination half-life of more than 24 hours
- drugs with an important time of onset of effect or rate of absorption
- critical dose drugs
- combination products
- drugs with highly variable pharmacokinetics
- drugs with measurable endogenous levels
- drugs for which pharmacodynamic studies are appropriate alternatives to comparative bioavailability studies of oral dosage formulations
- drugs for which urine drug concentration data is used

7. If applicable, specify which exemptive regulations were applied for:

12.(2) 
12.(3) 
12.(3.1) 
12.(4) 

Specify other applicable exemptive: ________________________________
SUBMISSION SUMMARY – PAGE 4

8. a) Clinical trials were conducted on the *submitted* product: ☐ ☐ ( )
   If not, please specify and provide justification:

b) Provide test product information: ☐ ☐ ( )
   1. Specify product name/generic name/strength/dosage form/package format and size

   2. Provided manufacturing master formulation documentation of the test product ☐ ☐ ( )

c) Is the name(s) of products evaluated in clinical trials different from that of the submitted product? ☐ ☐ ( )

d) If yes to (c), clarification/evidence linking the data to the submission is provided: ☐ ☐ ( )
   Formulation of the product provided ☐ ☐ ( )

e) Pharmacoeconomic analysis provided: ☐ ☐ ( )
   If no, please provide justification:

f) Three year financial impact analysis provided: ☐ ☐ ( )

g) Pharmacoeconomic analysis summary provided: ☐ ☐ ( )
**CLINICAL DATA CHECKLIST**

**Manufacturer Name:** ________________________________

**Drug Product Name/ generic name/ strength/ dosage form/ package format and size:**

<table>
<thead>
<tr>
<th>Drug Product</th>
<th>Page Ref(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What is the pharmacological mechanism of the drug?</td>
<td></td>
</tr>
<tr>
<td>2. What are the drug's Health Canada approved indications?</td>
<td></td>
</tr>
<tr>
<td>3. What is the recommended dose range and duration of therapy? (Please include relevant patient populations - e.g., the elderly)</td>
<td></td>
</tr>
<tr>
<td>4. What Formulary/CDI listing status is proposed by the manufacturer?</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical Evidence**

1. What are the conclusions of randomized controlled trials supporting the efficacy (i.e. when used under optimal circumstances) of the product? Are trials published in peer-reviewed journals?

2. What are the key comparators for this drug product? Which ones are listed in the Formulary/CDI?
3. What are the results of randomized trials comparing the product to listed alternatives on the Formulary/CDI? Are there randomized trials comparing the product to the least costly and most widely used alternative products listed in the Formulary/CDI?

4. What are the conclusions of randomized controlled trials supporting the effectiveness (i.e., when used under usual, real world circumstances) of the product? Are trials published in peer-reviewed journals?

5. Do the randomized trials use the most clinically relevant outcome measures, or do they use the surrogate outcomes requiring extrapolation to the relevant outcome? Are the end-point(s) sufficiently justified?

6. Were any clinical studies conducted in the elderly, women and children? If not, why not?

7. Were any of the clinical trials conducted in Canada?

8. Are there ongoing trials that would provide additional information on the product?

9. What are the contraindications for the product?

10. What are the side effects of the drug product?
11. Are there particular safety issues of concern to recipients of the ODB program (e.g., safety in the elderly, women and children)?

12. If the product contains a combination of drugs, is there a pharmacologic and pharmacokinetic rationale for the combination? Specifically, does each component of the combination make a contribution to the claimed effect(s)? Is the dose of each component appropriate for the elderly and/or children? Is the effect of either component modified (synergistically or antagonistically) by the addition of the other component?
Drugs Utilization

1. What are the Health Canada approved patient population group(s) for the drug? 

2. Will clinicians be able to easily and precisely determine which patients should be treated with this drug? Please explain.

3. Are there other clinical uses or trials for non-approved Health Canada indications?

4. Is it likely that clinicians will expand the use of the product for conditions not approved by Health Canada? If not, what is the evidence to support this position?

5. What is the projected number of patients in Ontario covered by ODB who will use the product in a year?

6. Are there utilization data for the drug product in other jurisdictions? If so, please discuss the possible utilization impact for ODB.
### SECTION I. DRUG PRODUCT

**Product Information**

<table>
<thead>
<tr>
<th>Brand Name / Manufacturer</th>
<th>Drug X Tablet USP (ACME Ltd.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic Name / Strength / Dosage Form</td>
<td>Generic C 5 mg Tablet</td>
</tr>
<tr>
<td>DIN</td>
<td>01234567</td>
</tr>
<tr>
<td>Usual Dose Regimen/Duration</td>
<td>5 mg bid x 10 days</td>
</tr>
<tr>
<td>Submitted Proposed Drug Benefit Price Per Unit</td>
<td>$2.00 per tab</td>
</tr>
<tr>
<td>Daily Cost *</td>
<td>$ 4.00 per day</td>
</tr>
</tbody>
</table>

* based on usual dosing regimen and submitted price, as stated above

<table>
<thead>
<tr>
<th>Available Package Size (A)</th>
<th>Price (B)</th>
<th>Calculated Price/Unit (C = B/A)</th>
<th>Cost of Usual Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>$ 100.00</td>
<td>$ 2.00 per tablet</td>
<td>$ 40.00</td>
</tr>
<tr>
<td>100</td>
<td>$200.00</td>
<td>$ 2.00 per tablet</td>
<td>$ 40.00</td>
</tr>
<tr>
<td>500</td>
<td>$1000.00</td>
<td>$ 2.00 per tablet</td>
<td>$ 40.00</td>
</tr>
</tbody>
</table>
SECTION II. COMPARATOR DRUG PRODUCT / TREATMENT

Please indicate all appropriate drug comparators (including strength and dosage form) and/or treatment comparators for this product.

<table>
<thead>
<tr>
<th>Generic Name (Mfr) / Strength / Dosage Form</th>
<th>Price *</th>
<th>Equivalent Dosing Regimen for Comparator</th>
<th>Daily Cost</th>
<th>Cost of Usual Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic A (Brand Y Inc) 5 mg USP tab</td>
<td>$1.00</td>
<td>5 mg bid x 10 days</td>
<td>$2.00</td>
<td>$20.00</td>
</tr>
<tr>
<td>Generic B (Brand Z Inc) 5 mg BP cap</td>
<td>$1.50</td>
<td>5 mg tid x 7 days</td>
<td>$4.50</td>
<td>$31.50</td>
</tr>
</tbody>
</table>

* indicate source if other than the price in the Formulary/CDI.

SECTION III. COMPARATIVE OUTCOMES

<table>
<thead>
<tr>
<th>Drug</th>
<th>Outcome 1 (e.g. successes)</th>
<th>Outcome 2 (e.g. adverse events)</th>
<th>Outcome 3 (e.g. deaths)</th>
<th>Outcome 4 (e.g. projected survival)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug X</td>
<td>$70%</td>
<td>5%</td>
<td>1%</td>
<td>20 years</td>
</tr>
<tr>
<td>Generic A</td>
<td>$80%</td>
<td>10%</td>
<td>2%</td>
<td>18 years</td>
</tr>
<tr>
<td>Generic B</td>
<td>$70%</td>
<td>10%</td>
<td>3%</td>
<td>16 years</td>
</tr>
</tbody>
</table>

References:

Note:

- Appropriate comparators should be listed for each strength and dosage form.

- The manufacturer should indicate comparable dosing regimens, including the duration of therapy.
• Where there are multiple source alternatives for the products, the lowest cost interchangeable alternatives should be listed first.

• Where there are listed single source alternatives for the product, these may also be listed.

• Where there are no appropriate listed single or multiple source alternatives, other marketed drug products may be listed.

• Where the appropriate comparison is not a drug but another treatment, please attach a separate sheet outlining the treatment and indicating why it is the appropriate comparator.

SECTION IV. PHARMACOECONOMIC ANALYSIS

Pharmacoeconomic Analysis included? [ ] Yes [ ] No

Pharmacoeconomic Analysis Worksheet included?[ ] Yes [ ] No

If yes, please indicate type of analysis: [ ] Cost-Minimization

[ ] Cost-Consequence

[ ] Cost-Effectiveness

[ ] Cost-Utility

[ ] Cost-Benefit

If a detailed economic analysis is not included, please outline the reasons below:
Please complete each of the following questions:

1. (a) What is the question being asked in the analysis?
   (b) What type of economic analysis was performed to answer the question?
   i. Cost comparison
   ii. Cost-consequence analysis
   iii. Cost-effectiveness analysis
   iv. Cost-utility analysis
   v. Cost-benefit analysis
   (c) What is the justification for the approach taken?

2. (a) Did the study involve a comparison of alternative treatments for patients with the same clinical condition?
   (b) Are those alternatives explicitly stated?
   (c) Is the analysis therefore an incremental analysis?

3. (a) Is the viewpoint or perspective for the analysis stated clearly?
   (b) Is it a societal perspective, third-party payer perspective, patient perspective?
   (c) Is the analysis presented in a disaggregated fashion showing these perspectives separately?

4. (a) Was the evidence of the product's efficacy established through randomized trials?
   (b) Was this evidence of efficacy supplemented by evidence of effectiveness applicable to the patients covered by the Ontario Drug Benefit program?
(c) Was the latter evidence derived from studies documenting routine use in clinical practice?

5. (a) Are the methods and analysis displayed in a clear and transparent manner?
    (b) Are the components of the numerator (cost of each alternative) and denominator (clinical outcomes of each alternative) displayed?
    (c) Are clinical outcomes expressed first in natural units and then translated into alternative units such as benefits or utility? (See Section 3.4.d. of the Ontario Guidelines for Economic Analysis of Pharmaceutical Products for suggested format)

6. Are all important and relevant costs and consequences (outcomes), including adverse effects, for each alternative identified?

7. (a) Are costs and consequences modelled as in a decision tree with information derived from a variety of sources; OR
    (b) estimated directly from a variety of sources; OR
    (c) estimated directly from a specific patient population?

8. (a) Are capital costs and overhead costs included as well as operating costs?
    (b) How were they measured?

9. How were indirect costs identified and estimated?

10. How was quality of life measured?

11. (a) What equity assumptions were made in the analysis?
    (b) For example, are QALYs gained by any individual considered equal?

12. (a) If some variables were difficult to measure, how did the authors handle this difficulty?
    (b) Did they slant the analysis all in favour of one intervention in order to bias the analysis against the desired result?

13. (a) Were extensive sensitivity analyses performed?
(b) What were the ranges of values for variables in the sensitivity analyses?

14. (a) Is quality of life an important component of an economic analysis of this question?
   (b) How sensitive is the estimate of cost utility to variations in quality of life?

15. (a) Is there an estimate of the aggregate incremental expenditure required for the province to provide this product to patients covered by its programs?
   (b) What is the estimate of aggregate incremental costs?
   (c) Does this estimate cover all of the major indications for use of the product?

16. (a) Has the incremental cost-effectiveness ratio been estimated for a special clinical indication that represents the majority or all of its expected use by those covered under the Ontario Drug Benefit program?
   (b) Do these other indications involve a large amount of utilization for which the ratio may be very different?

17. (a) Who performed the analysis?
   (b) Did the authors of the report sign a letter indicating their agreement with the entire document presented?
   (c) Does the report indicate that the authors had independent control over the methods and right to publish the analysis regardless of its results?

18. What is the "bottom line" result of the analysis in quantitative terms? The answer to this question will be statements like the following:
   - The cost per QALYs gained for using this product compared to the alternative is $X, or ranges from $Y to $Z.
   - The use of this product compared to the stated alternative will result in an expected incremental expenditure of $X per patient treated with a net reduction of Y major adverse clinical events (e.g., cardiac deaths) and Z minor clinical events (e.g., side effects).
## SECTION I. DRUG PRODUCT

### Product Information

<table>
<thead>
<tr>
<th>Product Information</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Name / Manufacturer</td>
<td></td>
</tr>
<tr>
<td>Generic Name / Strength / Dosage Form</td>
<td></td>
</tr>
<tr>
<td>Proposed reimbursement status</td>
<td></td>
</tr>
<tr>
<td>DIN</td>
<td></td>
</tr>
<tr>
<td>Submitted Proposed Drug Benefit Price Per Unit</td>
<td></td>
</tr>
<tr>
<td>Daily Cost *</td>
<td></td>
</tr>
<tr>
<td>Usual Dosing Regimen/Duration</td>
<td></td>
</tr>
<tr>
<td>Maximum Dosing Regimen/Duration</td>
<td></td>
</tr>
</tbody>
</table>

* based on usual dosing regimen and submitted price, as stated above.

## SECTION II. SUMMARY OF ODB FINANCIAL IMPACT

<table>
<thead>
<tr>
<th>Summary Item</th>
<th>Manufacturer's Submitted Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 1</td>
</tr>
<tr>
<td>Drug Cost* ($)</td>
<td></td>
</tr>
<tr>
<td>Claims</td>
<td></td>
</tr>
<tr>
<td>Net Expenditure/(Savings)</td>
<td></td>
</tr>
</tbody>
</table>

* Drug Cost should exclude up-charge and professional fee.
SECTION III: UNDERLYING ASSUMPTIONS FOR KEY FACTORS IN FORECAST – MOST LIKELY SCENARIO

For each parameter, it would be helpful to organize the data according to Baseline (where applicable), Year 1, Year 2, and Year 3 with the confidence level (high, medium or low) and the evidence/data sources.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Confidence Level (high/med/low)</th>
<th>Evidence used to support assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Disease Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e.g. number of patients with the disease, number of patients consulting physicians, number of patients diagnosed, number of patients treated, number of ODB recipients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2. Market Share</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>For (1) submitted product;</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(2) comparators within therapeutic class;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3) other relevant comparators for therapeutic indication.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e.g. new patients, patients switching from competitor products)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parameter</td>
<td>Baseline</td>
<td>Year 1</td>
<td>Year 2</td>
<td>Year 3</td>
<td>Confidence Level (high/med/low)</td>
<td>Evidence used to support assumptions</td>
</tr>
<tr>
<td>-----------</td>
<td>----------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>---------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>b) Claims</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e.g. claims/ patient, claims/year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Growth Rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e.g., compliance rate, withdrawal rate, potential impact of future listings such as new generic products)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4. ODB Expenditures</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>For (1) submitted product;</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>(2) comparators within therapeutic class;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>(3) other relevant comparators for therapeutic indication.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>a) Cost per claim</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e.g. doses per day, cost per dose, cost per day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) ODB claims per year</td>
<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>c) Total expenditures</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>d) Net impact</td>
<td></td>
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</tr>
</tbody>
</table>
SECTION IV. CONTINGENCY ESTIMATES – PESSIMISTIC AND OPTIMISTIC SCENARIOS

For each parameter, it would be helpful to organize the data according to Baseline (where applicable), Year 1, Year 2, and Year 3 with the confidence level (high, medium or low) and the evidence/data sources.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Confidence Level (high/med/low)</th>
<th>Evidence used to support assumptions</th>
</tr>
</thead>
</table>

**PESSIMISTIC SCENARIO (SUBMITTED PRODUCT PERFORMANCE IS BELOW EXPECTATIONS)**

- Total annual ODB expenditure (submitted product) ($)
- Incremental change vs. most likely forecast ($)
- Total ODB expenditure (therapeutic class) ($)
- Incremental change vs. most likely forecast ($)
- Rationale for changes (list/identify any significant modifications in assumptions)

**OPTIMISTIC SCENARIO (SUBMITTED PRODUCT PERFORMANCE EXCEEDS EXPECTATIONS)**

- Total annual ODB expenditure (submitted product) ($)
- Incremental change vs. most likely forecast ($)
- Total ODB expenditure therapeutic class) ($)
- Incremental change vs. most likely forecast ($)
- Rationale for changes (list/identify any significant modifications in assumptions)
SUBMISSION SUMMARY
For Submissions under DIDFA, Regulation 935

<table>
<thead>
<tr>
<th>Drug Products (Brand name/generic name/strengths/package format and size):</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Original/Innovator Drug Product (to which interchangeability designation is sought)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Submitting Manufacturer:</th>
</tr>
</thead>
</table>

Please complete all items

Submission Type

1. Submission Type (select one)
   - First Review
   - Reconsideration

2. Category/Designation
   a) Submission category (select one)
      - New Product
      - New Strength
      - New Indication
      - New Dosage
      - New Format
      - Notice of Change
      - OTC drug product
      - Natural Health Product
      - SDP Drug Product

b) If applicable, list Formulary designation sought:
   - ODB Interchangeable
   - OFI Listing
   - Facilitated Access
   - EAP
   - CCO-ODB
3. **Rapid Review Request** (not applicable for multiple source product submission)

4. **Source and Authorization for Submission**
   a) Submitting manufacturer of the submission indicated: ☐ ☐ ( )
   b) Is the submitting manufacturer the holder of the Notice of Compliance (NOC)?
      *If not, provide information for 4. (c) and (d)*
      ☐ ☐ ( )
   c) Letter from NOC holder authorizing submitting manufacturer
      to submit on NOC holder’s behalf:
      ☐ ☐ ( )
   d) Business relationship/ agreement between each party detailed:
      ☐ ☐ ( )
   e) Product Confirmation Letter from all parties
      ☐ ☐ ( )

5. **Administrative Issues**
   a) Two complete sets of the submission provided:
      ☐ ☐
   b) Number of binders that make up each set of a submission:
      ( )
   c) Submission is well organized, tabbed and indexed according to the
      relevant section of the requirements:
      ☐ ☐
   d) A table of contents is included in the submission:
      ☐ ☐

6. **Submission Data**
   a) Drug Product Dosage Form: Immediate Release ☐ Modified Release ☐
      Solid Oral Dosage Form
      Solution ☐ Aqueous ☐ Non-Aqueous ☐
      Cream ☐ Ointment ☐
      Suspension ☐
      Other ☐ Specify __________________________
   b) Drug Status
      New Drug ☐ ☐
- Drugs that met Health Canada's bioequivalence standards
- Drugs with one or more of the following characteristics (i.e., exceptions that require modifications to Health Canada's standards):
  - modified-release dosage forms
    - drugs with serious toxicity within the normal dosage range
    - drugs exhibiting non-linear pharmacokinetics
    - drugs with a terminal elimination half-life of more than 24 hours
    - drugs with an important time of onset of effect or rate of absorption
  - critical dose drugs
  - combination products
  - drugs with highly variable pharmacokinetics
  - drugs with measurable endogenous levels
  - drugs for which pharmacodynamic studies are appropriate alternatives to comparative bioavailability studies of oral dosage formulations
  - drugs for which urine drug concentration data is used

7. If applicable, specify which sections in Regulation 935 under DIDFA apply:

<table>
<thead>
<tr>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.(2)</td>
</tr>
<tr>
<td>6.(3)</td>
</tr>
<tr>
<td>6.(4)</td>
</tr>
<tr>
<td>6.(5)</td>
</tr>
<tr>
<td>6.(5.1)</td>
</tr>
<tr>
<td>6.(6)</td>
</tr>
<tr>
<td>6.(7)</td>
</tr>
<tr>
<td>7.1</td>
</tr>
<tr>
<td>7.2</td>
</tr>
</tbody>
</table>

Comparable dosage □ Specify: ________________________________
Similar active ingredient  ☐ Specify:__________________________

SUBMISSION SUMMARY – PAGE 4

1. **Interchangeability Information**
   
   a) Bioequivalence declared to the Canadian Reference Product on the NOC:
      □  □  (  )
   
   b) Reference product is the same as the ministry’s original/innovator product:
      □  □  (  )
   
   c) Reference product is currently listed in the Formulary
      □  □  
   
   d) If reference product is not currently listed in the Formulary, specify the edition, supplement, and page number indicating when the original/innovator product was first listed.
      
      Edition:  (  )
      
      Supplement:  (  )
      
      Page:  (  )
   
   e) Reference product is a non-Canadian reference product (NCRP)  □  □
      
      List reference product name and country of NCRP: __________________________
      
      Justification and/or evidence provided for use of NCRP  □  □
   
   f) OFI Reference Product information provided:
      □  □  (  )

9. **Bioavailability Data**

   a) Bioavailability study report provided:
      □  □  (  )
      
      If not, please provide justification/exemption:
      (  )
   
   b) Bioavailability test lots have the same formulation as the submitted lot:
      □  □  (  )
   
   c) Clarification/evidence provided of linkage if product names different in (b)
      □  □  (  )
   
   d) Master formulation of the biolot provided
      □  □  (  )
## BIOEQUIVALENCE DATA CHECKLIST

**Product Name/Generic Name/Strength/Dosage Form/Package Size:**

<table>
<thead>
<tr>
<th>Manufacturer:</th>
<th>Page Ref(s)</th>
</tr>
</thead>
</table>

(a) Executive summary of findings from the bioequivalence study (a short abstract giving the arguments for considering the products interchangeable), including a brief summary of the protocol, if available.

(b) Original study protocol.

(c) Name of test drug product/generic name/strength/dosage form/package format and size, lot number and expiry date

(d) Name of reference drug product/generic name/strength/dosage form/package format and size, lot number and expiry date

(e) Date(s) and site of study

(f) List of investigators and affiliations (CVs should be attached as appendix to study, as opposed to the main submission).

(g) List, with reasons, any protocol violations and/or missing values
(h) If requesting listing of more than one strength, indicate proportionality with tested strength; if not proportional, indicate if changes are significant, with supporting documentation.

(i) Description and method validation, including coefficient of variation, of the analytical method used in the bioavailability study.

(j) Pharmacodynamic data, if any, with appropriate statistical analysis and relationship to the pharmacokinetic data.

(k) Data on all subjects:

- age, sex and any other demographic information deemed relevant.

- AUCt, AUC’s, Cmax, Tmax and any other pharmacokinetic parameters computed from potency corrected data for the drug products tested.

- time-concentration curve calculated with potency uncorrected data for each individual, for the drug products tested.

- adverse reactions, if any, tabulated by drug product.
(l) Data analysis:

- Means, standard deviations, coefficient of variations for each of the parameters, by drug product.

- Analysis of Variance used to derive the standard error in computing the confidence interval, including sources of variation for drug period, sequence and subjects within sequence.

- 90% confidence intervals on the appropriate scale for the ratios of the means for AUCt, AUC’s, Cmax.

- A statement of conclusion and reasons for the conclusion.

(m) Other relevant data/information (please describe).

Note: The ministry has harmonized its practices with the Therapeutic Product Programme (TPP) of Health Canada, and has the same statistical requirements for AUC and Cmax for drugs with uncomplicated characteristics. The following statistical requirements are used to assess the bioavailability studies for drugs with uncomplicated characteristics: confidence intervals for AUC at the 90% level, and comparison of mean Cmax.
<table>
<thead>
<tr>
<th>Test Product Information</th>
<th>Reference Product Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manufacturer Name of test product</strong></td>
<td><strong>Manufacturer Name of reference product</strong></td>
</tr>
<tr>
<td>Name of drug product/generic name/strength/dosage form/package format and size</td>
<td>Name of original product (Reference)/generic name/strength/dosage form/package format and size</td>
</tr>
<tr>
<td>lot number: expiry date:</td>
<td>lot number: expiry date:</td>
</tr>
</tbody>
</table>
Reviewer:

<table>
<thead>
<tr>
<th>AUC (0-T)</th>
<th>Test Product (Name/Strength/Dosage Form)</th>
<th>Reference Product (Name/Strength/Dosage Form)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>20.12</td>
<td>19.04</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>14.04</td>
<td>13.21</td>
</tr>
<tr>
<td>Coefficient of Variation</td>
<td>69.80</td>
<td>69.38</td>
</tr>
<tr>
<td>Ratio of Means</td>
<td>105 %</td>
<td></td>
</tr>
<tr>
<td>Mean of Ratios</td>
<td>107 %</td>
<td></td>
</tr>
<tr>
<td>90% Confidence Interval (potency corrected)</td>
<td>95 - 115 %</td>
<td></td>
</tr>
</tbody>
</table>

ANOVA (S/NS) Subject [S] Treatment [N/S] Sequence [N/S]

<table>
<thead>
<tr>
<th>Distribution of individual ratios (# subjects test vs. ref.)</th>
<th>&lt;0.7</th>
<th>0.7-0.8</th>
<th>0.8-0.9</th>
<th>0.9-1.1</th>
<th>1.1-1.2</th>
<th>1.2-1.3</th>
<th>&gt;1.3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>AUC (0-4)</td>
<td>Test Product (Name/Strength/Dosage Form)</td>
<td>Reference Product (Name/Strength/Dosage Form)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>------------------------------------------</td>
<td>-----------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>21.54</td>
<td>20.39</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>14.24</td>
<td>13.37</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coefficient of Variation</td>
<td>66.11</td>
<td>65.57</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ratio of Means</td>
<td>105.0 %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean of Ratios</td>
<td>107.0 %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90% Confidence Interval</td>
<td>96.0 - 115.0 %</td>
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</tbody>
</table>

ANOVA (S/NS) Subject [ S ] Treatment [ N / S ] Sequence [ N / S ]

<table>
<thead>
<tr>
<th>Distribution of individual ratios (# subjects test vs. ref.)</th>
<th>&lt;0.7</th>
<th>0.7-0.8</th>
<th>0.8-0.9</th>
<th>0.9-1.1</th>
<th>1.1-1.2</th>
<th>1.2-1.3</th>
<th>&gt;1.3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>2</td>
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</table>
## PHARMACOKINETIC/STATISTICAL WORK SHEET – PAGE 4

<table>
<thead>
<tr>
<th>Cmax</th>
<th>Test Product</th>
<th>Reference Product</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Name/Strength/Dosage Form)</td>
<td>(Name/Strength/Dosage Form)</td>
</tr>
<tr>
<td>Mean</td>
<td>12.16</td>
<td>11.55</td>
</tr>
<tr>
<td>SD</td>
<td>7.85</td>
<td>8.68</td>
</tr>
<tr>
<td>CV</td>
<td>64.56</td>
<td>75.13</td>
</tr>
<tr>
<td>Ratio of Means</td>
<td>103.0 %</td>
<td></td>
</tr>
<tr>
<td>Mean of Ratios</td>
<td>110.0 %</td>
<td></td>
</tr>
<tr>
<td>90% CI (potency corrected)</td>
<td>89.0 - 120.0 %</td>
<td></td>
</tr>
</tbody>
</table>

ANOVA (S/NS) Subject [ S ] Treatment [ N / S ] Sequence [ N / S ]

<table>
<thead>
<tr>
<th>Distribution of individual ratios (# subjects test vs. ref.)</th>
<th>&lt;0.7</th>
<th>0.7-0.8</th>
<th>0.8-0.9</th>
<th>0.9-1.1</th>
<th>1.1-1.2</th>
<th>1.2-1.3</th>
<th>&gt;1.3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Tmax</td>
<td>Test Product (Name/Strength/Dosage Form)</td>
<td>Reference Product (Name/Strength/Dosage Form)</td>
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<td>----------</td>
<td>----------------------------------------</td>
<td>----------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.58</td>
<td>0.50</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
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<td>0.27</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Coefficient of Variation</td>
<td>41.05</td>
<td>41.26</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
## DRUG SUBMISSION SCREENING CHECKLIST FOR AQUEOUS SOLUTIONS*

*adapted from Health Canada’s *Pharmaceutical Quality of Aqueous Solutions (2005)*

<table>
<thead>
<tr>
<th>Drug Product Information</th>
<th>Reference Product Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug product: product name (chemical name/strength/dosage form)</td>
<td>Reference product: product name (chemical name/strength/dosage form)</td>
</tr>
<tr>
<td>Lot number:</td>
<td>Lot number:</td>
</tr>
<tr>
<td>Expiry date:</td>
<td>Expiry date:</td>
</tr>
<tr>
<td>Package size:</td>
<td>Package size:</td>
</tr>
</tbody>
</table>

### Testing Parameter

<table>
<thead>
<tr>
<th>Testing Parameter</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UNIVERSAL TESTS (generally applicable to all dosage forms)</strong></td>
<td></td>
</tr>
<tr>
<td>Description, colour, clarity, expiry</td>
<td>S,C</td>
</tr>
<tr>
<td>Assay (drug substance), Potency</td>
<td>S</td>
</tr>
<tr>
<td><strong>SPECIFIC TESTS (specific to individual dosage forms)</strong></td>
<td></td>
</tr>
<tr>
<td>Microbial Limits (USP &lt;61&gt;) (if product is not sterile)</td>
<td>S</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Uniformity of Dosage Units (USP &lt;905&gt;) (if packaged in a single-unit container)</td>
<td>S</td>
</tr>
<tr>
<td>Delivered Dose Uniformity (USP &lt;601&gt;) (if packaged with a device for delivery)</td>
<td>N/A</td>
</tr>
<tr>
<td>Antimicrobial Preservative Content (if present)</td>
<td>S</td>
</tr>
<tr>
<td>Antimicrobial Preservative Effectiveness (if present) (USP &lt;51&gt;)</td>
<td>D</td>
</tr>
<tr>
<td>Potency, Salt, Solvent</td>
<td>C</td>
</tr>
<tr>
<td>Viscosity (USP &lt;911&gt;)</td>
<td>C</td>
</tr>
<tr>
<td>Specific Gravity or Density (USP &lt;841&gt;)</td>
<td>C</td>
</tr>
<tr>
<td>Osmolality (mol/kg) / Osmolarity (mol/L) (if tonicity is declared on the product labelling) (USP &lt;785&gt;)</td>
<td>N/A</td>
</tr>
<tr>
<td>Surface Tension</td>
<td>C</td>
</tr>
<tr>
<td>Buffering Capacity (if product contains a buffer)</td>
<td>D,C</td>
</tr>
<tr>
<td>Particulate Matter (USP &lt;788&gt; / &lt;789&gt;)</td>
<td>N/A</td>
</tr>
<tr>
<td>Sterility (if sterility is declared on the product labelling) (USP &lt;71&gt;)</td>
<td>S</td>
</tr>
</tbody>
</table>

Ontario Guidelines for Drug 300 September 2016
Submission and Evaluation
<table>
<thead>
<tr>
<th>Testing Parameter</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial Endotoxins / Pyrogens (USP &lt;85&gt; / USP &lt;151&gt;)</td>
<td>N/A</td>
</tr>
<tr>
<td>Distribution Coefficient</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**CONTAINER CLOSURE SYSTEM TESTS**

| Deliverable Volume, Minimum Fill, or Volume for Injection (if applicable) (USP <698>, USP <755>, or USP <1>) | S | S | S | D | D | S |
| Droplet Size or Volume (if administered as drops) | D,C | D,C | D,C | N/A | N/A | N/A |
| Droplet Size Distribution (if administered as a spray) | D,C | D,C | D,C | D,C | D,C | N/A |
| Device Attributes (if applicable) | D | D | D | D,C | D,C | D |

S = generally included in the finished product release specifications  
D = generally performed during pharmaceutical development  
C = generally included in a comparative study of the physicochemical properties  
N/A = not applicable or not required

* orally administered solutions may be either aqueous or alcohol-based; all other solutions, regardless of the route of administration, must be aqueous.

PART VIII

NEW POLICY DIRECTIVES
From time to time, notices may be posted on the website or manufacturers may receive correspondence outlining new policy directives issued by the Ontario Public Drug Programs. For easy reference, this section can be used for filing information relating to the drug submission review process.
PART IX

INTERPRETATION BULLETINS
From time to time and as circumstances warrant, the ministry may be required to amend or institute new policies, practices or procedures relating to drug submissions and the review process. The ministry will provide manufacturers with notice of such changes through “Interpretation Bulletins” which will be published electronically on the OPDP Notice and the ministry website.

Should there be any inconsistencies or conflicts as between the Guidelines and the Interpretation Bulletin, the more recent document (i.e. the Interpretation Bulletin) will prevail.

It is the responsibility of manufacturers to monitor amendments to the Guidelines through the OPDP Notice and the ministry website.
PART X

LONG-ACTING OXYCODONE PRODUCTS
O. Reg. 201/96 under ODBA

1(1.2) The executive officer shall not, under section 16 of the Act, make the Act apply in respect of a drug that is a drug product described in subsection 12 (9) of this Regulation, unless the conditions set out in that subsection are met.

12. (9) A strength and dosage form of a drug product that contains oxycodone as the only active ingredient and that is a long-acting product that has been formulated in a solid dosage form for oral administration shall not be designated as a listed drug product unless the following conditions are met:

1. There must be evidence satisfactory to the executive officer that the drug product exhibits one or more physiochemical properties that, when compared to drugs without the property or properties, make the drug product,

   i. significantly more difficult to alter, break, crush, chew, dissolve or otherwise manipulate in such a way that it could be misused, abused or put to an intended use that is different than the use for which it is prescribed, or

   ii. significantly less effective and less likely to be misused, abused or put to an intended use that is different than the use for which it is prescribed, if the product is altered, broken, crushed, chewed, dissolved or otherwise manipulated.

2. The evidence referred to in paragraph 1 must be demonstrated by,

   i. in vitro testing,

   ii. in vivo testing,

   iii. another form of testing of equivalent reliability, or

   iv. a combination of any of the forms of testing mentioned in subparagraphs i to iii. O. Reg. 20/13, s. 2.

Regulation 935 under DIDFA

6. (8) A strength and dosage form of a drug product that contains oxycodone as the only active ingredient and that is a long-acting product that has been formulated in a solid dosage form for oral administration shall not be designated as interchangeable
unless the following conditions are met:

1. There must be evidence satisfactory to the executive officer that the drug product exhibits one or more physiochemical properties that, when compared to drugs without the property or properties, make the drug product,
   
i. significantly more difficult to alter, break, crush, chew, dissolve or otherwise manipulate in such a way that it could be misused, abused or put to an intended use that is different than the use for which it is prescribed, or
   
ii. significantly less effective and less likely to be misused, abused or put to an intended use that is different than the use for which it is prescribed, if the product is altered, broken, crushed, chewed, dissolved or otherwise manipulated.

2. The evidence referred to in paragraph 1 must be demonstrated by,
   
i. in vitro testing,
   
ii. in vivo testing,
   
iii. another form of testing of equivalent reliability, or
   
iv. a combination of any of the forms of testing mentioned in subparagraphs i to iii. O. Reg. 21/13, s.1

Long-acting oxycodone products will not be considered for funding under the Ontario Drug Benefit Act (ODBA) unless they meet the criteria set out in subsection 12. (9) of O. Reg. 201/96 made under the ODBA.

No long-acting oxycodone products will be designated as an interchangeable product under the Drug Interchangeability and Dispensing Fee Act (DIDFA) unless it meets the criteria set out in subsection 6. (8) of Regulation 935 made under the DIDFA.

The ministry requires the manufacturer of a long-acting oxycodone product to provide evidence satisfactory to the ministry that the oxycodone product is manufactured in such a way to make it more difficult to alter, break, crush, chew, dissolve or otherwise manipulate; or less effective and less likely to be misused or abused, in the event that the product is altered, broken, crushed, chewed, dissolved, or otherwise manipulated.
PART XI

SUBMISSION GUIDELINES FOR
LONG-ACTING OXYCODONE PRODUCTS IN
SOLID ORAL DOSAGE FORM
Regulatory Requirements Impose Additional Conditions on Submissions for Long-Acting Oxycodone Drug Products

Subsections 1(1.2) and 12(9) of Ontario Regulation 201/96 made under the Ontario Drug Benefit Act ("ODBA") and subsection 6(8) of Regulation 935 made under the Drug Interchangeability and Dispensing Fee Act ("DIDFA") set out the following requirements:

O. Reg. 201/96 under ODBA

1(1.2) The executive officer shall not, under section 16 of the Act, make the Act apply in respect of a drug that is a drug product described in subsection 12 (9) of this Regulation, unless the conditions set out in that subsection are met.

12(9) A strength and dosage form of a drug product that contains oxycodone as the only active ingredient and that is a long-acting product that has been formulated in a solid dosage form for oral administration shall not be designated as a listed drug product unless the following conditions are met:

1. There must be evidence satisfactory to the executive officer that the drug product exhibits one or more physiochemical properties that, when compared to drugs without the property or properties, make the drug product,

   i. significantly more difficult to alter, break, crush, chew, dissolve or otherwise manipulate in such a way that it could be misused, abused or put to an intended use that is different than the use for which it is prescribed, or

   ii. significantly less effective and less likely to be misused, abused or put to an intended use that is different than the use for which it is prescribed, if the product is altered, broken, crushed, dissolved or otherwise manipulated.

2. The evidence referred to in paragraph 1 must be demonstrated by,

   i. in vitro testing,

   ii. in vivo testing,
iii. another form of testing of equivalent reliability, or

iv. a combination of any of the forms of testing mentioned in subparagraphs i to iii.

Regulation 935 under DIDFA

6(8) A strength and dosage form of a drug product that contains oxycodone as the only active ingredient and that is a long-acting product that has been formulated in a solid dosage form for oral administration shall not be designated as interchangeable unless the following conditions are met:

1. There must be evidence satisfactory to the executive officer that the drug product exhibits one or more physiochemical properties that, when compared to drugs without the property or properties, make the drug product,

i. significantly more difficult to alter, break, crush, chew, dissolve or otherwise manipulate in such a way that it could be misused, abused or put to an intended use that is different than the use for which it is prescribed, or

ii. significantly less effective and less likely to be misused, abused or put to an intended use that is different than the use for which it is prescribed, if the product is altered, broken, crushed, dissolved or otherwise manipulated.

2. The evidence referred to in paragraph 1 must be demonstrated by,

i. in vitro testing,

ii. in vivo testing,

iii. another form of testing of equivalent reliability, or

iv. a combination of any of the forms of testing mentioned in subparagraphs i to iii.

A manufacturer of a long-acting oral drug product that contains oxycodone as the only active ingredient is required to provide evidence satisfactory to the Executive Officer that the drug product meets the above regulatory requirements before the drug product
may be considered for public funding under the ODBA and/or be designated as an interchangeable product under the DIDFA.

The requirements may be satisfied by completing in vivo, or in vitro studies or both. In all these cases, the manufacturer must demonstrate that the drug product has physiochemical properties that, when compared to products without such properties, make the product more difficult to alter, break, crush, chew, dissolve or otherwise manipulate, or less effective and less likely to be misused or abused, in the event that the product is altered, broken, crushed, chewed, dissolved, or otherwise manipulated (hereinafter referred to as “abuse deterrent properties”).

**Evidence that the long-acting oxycodone product has abuse deterrent properties**

The manufacturer must satisfy this requirement by submitting the following:

- A full explanation of the formulation components that exhibit one or more physiochemical properties that, when compared to drugs without such properties, would make the manufacturer’s drug product more difficult to alter, break, crush, chew, dissolve or otherwise manipulate; or less effective and less likely to be misused or abused, in the event that the product is altered, broken, crushed, chewed, dissolved, or otherwise manipulated.

The manufacturer must submit the results of the following in vitro tests:

1. Resistance to particle size reduction.
2. Dissolution tests, after particle size reduction, in water, household solvents and buffers.
3. Physical properties of the resulting solution after particle size reduction and dissolution into a small volume of water.
4. Extraction into advanced solvents after particle size reduction.
5. Extraction following vaporization techniques.
6. Extraction and purification of the drug substance from the crushed dosage form using pH adjustment and solvent extraction or filtration.

The submission will be deemed incomplete if any of the above components are missing.

The assessment of whether the drug product has abuse deterrent properties that comply with the regulatory requirements will be based on the results of all of the above identified in vitro tests.
Manufacturers may conduct other tests or additional studies to support their submissions. Justification, methodology and results for each test must be documented fully.

This guideline will be updated periodically as appropriate based on evolving evidence in the field.

Manufacturers are encouraged to contact the ministry to discuss other tests, methodology and specifications, etc., prior to conducting additional tests not specified in this guideline.

### Points of Clarification

#### Formulation Composition

The manufacturer must submit the complete master formulation (CPID) for the drug product and an explanation on how the drug product exhibits one or more physiochemical properties that, when compared to drugs without such properties, would make the drug product more difficult to alter, break, crush, chew, dissolve or otherwise manipulate; or less effective and less likely to be misused or abused, in the event that the product is altered, broken, crushed, chewed, dissolved, or otherwise manipulated.

#### Evidence of Abuse Deterrent Properties

A complete description of the methods and results of the following tests must be submitted by the manufacturer to show how a new drug product with abuse deterrent properties is improved over a drug product without such properties, or to compare a second market entry product with abuse deterrent properties to a reference product with abuse deterrent properties that is funded under the ODBA and/or has been designated as interchangeable under the DIDFA.

All dosage strengths must be examined or justification provided that testing dosage strengths which bracket the available dosage strengths is representative of all dosage strengths.

The methods must be validated and described fully in the submission. The sample size will be a minimum of six (6) tablets for each test. Precision of the tests should be
sufficient to satisfy the requirement that the 90% confidence interval (CI) will be no greater than +/- 20%.

1. **Resistance to particle size reduction:**

   The ability to crush or pulverize the test and reference products by commonly available devices; hammer, pill crusher, knife, mortar and pestle, spoons, food grinder or other commonly available devices should be determined. The manufacturer must provide all tests listed * (see Appendix). The size of the resulting particles should be determined by sieving or other suitable means.

   Particle sizes should be categorized as whole deformed tablet, or as the proportion of tablet weight found as chunks, coarse powder, medium powder, and fine powder, or comparable and appropriate discrimination of particle sizes.

   **Acceptance Criteria:**

   i. When comparing a new abuse deterrent drug product to the reference abuse deterrent drug product, the test/reference (T/R) ratio of mean particle size must have a lower 90 % Confidence Interval greater than 80% and the width of the 90% CI must not exceed ±20%; and

   ii. When comparing a new abuse deterrent drug product to a drug product without the abuse deterrent properties, the manufacturer must provide descriptive statistics that demonstrate a significant difference in abuse-deterrence. The test/reference (T/R) ratio of mean particle size must have a lower 90 % Confidence Interval greater than 80% and the width of the 90% CI must not exceed ±20%.

2. **Dissolution tests, after particle size reduction, in water, household solvents and buffers.**

   The dissolution profiles of the test product following each method of particle size reduction completed above (hammer, pill crusher, coffee grinder etc.) should be compared to the dissolution profiles of the reference product following the same method of particle size reduction in water and common household solvents. Typical solvents will include: water, ethanol, acidic beverage, buffers at several pH values (1, 3, 7, 10) or other suitable solvents.
**Acceptance Criteria:**

i. When comparing a new abuse deterrent drug product to the reference abuse deterrent drug product, the f2 value for the dissolution comparison of comparing test to reference must be > 50, indicating similarity. f2 values indicating dissimilar dissolution profiles may be acceptable if it is also demonstrated that the test profile has reduced dissolution of the drug substance during the test; and

ii. When comparing a new abuse deterrent drug product to a drug product without the abuse deterrent properties, the f2 value for the dissolution comparison for test to reference should be <50 indicating dissimilarity

3. **Physical properties of the resulting solution after particle size reduction and dissolution into a small volume of water.**

   The drug substance in the crushed tablet should be dissolved in a small volume of water (5 and 10 ml) and the viscosity of the resulting solution determined and compared to the reference product.

   It may be sufficient to conduct this test on finely powdered fractions of the test and reference products.

**Acceptance criteria:**

i. When comparing a new abuse deterrent drug product to the reference abuse deterrent drug product, the lower limit of the 90% CI of the mean T/R viscosity must be greater than 80% and the Confidence Interval must have and a width not exceeding +/- 20%; and

ii. When comparing a new abuse deterrent drug product to a drug product without the abuse deterrent properties, the manufacturer must provide descriptive statistics and evidence that the T/R viscosity must be greater than 80% and the Confidence Interval must have and a width not exceeding +/- 20% - to confirm criteria with reviewer.
4. **Extraction into advanced solvents after particle size reduction.**

The amount of the drug substance extracted into 30 ml of solvent following each method of particle size reduction of the test product should be compared to amount of drug substance extracted following the same method of particle size reduction of the reference product. The amount of drug substance extracted should be determined after specified periods of time (e.g. 10 and 60 minutes). The test should be conducted at room temperature and at an elevated temperature.

Solvents might include: isopropyl alcohol 70%, paint thinner, other readily available solvents.

**Acceptance criteria:**

i. When comparing a new abuse deterrent drug product to the reference abuse deterrent drug product, the 90 % CI interval of the mean drug substance extracted T/R must have lower limit of the 90% CI greater than 80% and a width not exceeding +/- 20%; and

ii. When comparing a new abuse deterrent drug product to a drug product without the abuse deterrent properties, the manufacturer must provide descriptive statistics that demonstrate a significant difference. The upper 90% CI of the T/R ratio of the amount of drug substance recovered must not exceed 120% and the width of the 90% CI must not exceed +/- 20%.

5. **Extraction by vaporization**

It may be sufficient to conduct this test on the finely powdered material obtained from grinding the test and reference tablets. The finely powdered material should be heated in a system that is equipped with a device capable of trapping any volatilized drug substance. The temperature to which the material is subjected should be sufficient to vaporize the drug substance but not cause degradation. The time and temperature of vaporization should be reported. The amount of drug substance vaporized and the drug substance remaining in the residue after heating should be determined for the test and reference.
Acceptance Criteria:

i. When comparing a new abuse deterrent drug product to the reference abuse deterrent drug product, the amount vapourized must have an upper 90% CI not exceeding 120% and the width of the CI must not exceed +/- 20%; and

ii. When comparing a new abuse deterrent drug product to a drug product without the abuse deterrent properties, the manufacturer must supply descriptive statistics that demonstrate resistance to abuse by vaporization. The upper 90% CI of the T/R ratio of the amount of drug substance recovered must not exceed 120% and the width of the 90% CI must not exceed +/- 20%.

6. Extraction and Purification of the drug substance from the crushed tablet material using free-basing and filtration or solvent extraction.

The finely powdered tablet material should be dissolved in a small volume of water or 30 ml 0.1 N HCl. The pH of the extract should be adjusted to precipitate the free base, pH >9. The mixture is then filtered to collect the free base of the drug substance. This test should be conducted at room temperature and after cooling the basic solution.

To determine the ability to recover the drug substance with solvent extraction, the crushed tablet material should be extracted with 0.1 N HCl, the solution filtered and the pH of the filtrate adjusted to >9 with NaOH and commonly available solvents used to extract the free base from the aqueous solution. The resultant residue after solvent evaporation should be assayed for drug substance content.

Acceptance Criteria:

i. When comparing a new abuse deterrent drug product to the reference abuse deterrent drug product, the upper 90% CI of the T/R ratio of the amount of drug substance recovered must not exceeding 120% and the width of the 90% CI must not exceed +/- 20%; and

ii. When comparing a new abuse deterrent drug product to a drug product without abuse deterrent properties, the manufacturer must provide descriptive statistics that demonstrate a difference between the amount of drug substance recovered from the test and reference. The upper 90% CI of the T/R ratio of the amount of drug substance recovered must not exceed 120% and the width of the 90% CI must not exceed +/- 20%.
Note: Where applicable, raw data and a quantification of deviations between individual samples should be provided.

If certain information or data are not provided in the submission, an adequate justification must be given by the manufacturer or the submission will be deemed incomplete and will not proceed further in the review process.

**Format and Organization of Submissions**

Submissions must follow the same format and organization as described in Part II of the submission guidelines. In order to organize a submission in a manner that will facilitate review, submissions must be clearly tabbed in order, according to the headings of the submission requirements for diabetic testing agents as outlined above. Disorganized or incomplete submissions may be returned at the discretion of the ministry, at the manufacturer’s expense, without prejudice to refiling.
* Appendix

Table 1. Specifications for Each Device in Particle Size Reduction Tests.

<table>
<thead>
<tr>
<th>Device</th>
<th>Duration of Technique</th>
<th>Change with Abuse Deterrent Formulation</th>
<th>Change with Non-Abuse Deterrent Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 spoons</td>
<td>30 seconds</td>
<td>No change</td>
<td>Powder</td>
</tr>
<tr>
<td>Cheese grater (e.g. parmesan)</td>
<td>30 seconds</td>
<td>No change</td>
<td>powder</td>
</tr>
<tr>
<td>Manual spice or food grinder</td>
<td>30 seconds</td>
<td>No change</td>
<td>Powder</td>
</tr>
<tr>
<td>Electric Pepper Mill</td>
<td>30 seconds</td>
<td>No change</td>
<td>Powder</td>
</tr>
<tr>
<td>Electric Mini Food Processor-</td>
<td>30 seconds</td>
<td>No change</td>
<td>Powder</td>
</tr>
<tr>
<td>Manual Pill Crusher</td>
<td>30 seconds</td>
<td>Flattened deformed</td>
<td>Powder</td>
</tr>
<tr>
<td>Hammer</td>
<td>30 seconds</td>
<td>Flattened</td>
<td>Powder</td>
</tr>
<tr>
<td>Ceramic Mortar and Pestle</td>
<td>60 seconds</td>
<td>Flattened, broken, pieces</td>
<td>Powder</td>
</tr>
<tr>
<td>Chopped with 7 inch kitchen knife and Sliced with a razor blade</td>
<td>180 seconds</td>
<td>Small pieces</td>
<td>Small pieces</td>
</tr>
<tr>
<td>Electric Coffee Bean Grinder</td>
<td>180 seconds or specify duration to attain particle size</td>
<td>Small pieces</td>
<td>Small pieces</td>
</tr>
<tr>
<td>Electric Coffee Bean Grinder</td>
<td>45 seconds or specify duration to attain particle size</td>
<td>Powder</td>
<td>Powder</td>
</tr>
</tbody>
</table>