

Ministry of Health
and Long-Term Care

Ontario Public Drug Programs

Office of the Executive Officer
and Assistant Deputy Minister

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Ministère de la Santé
et des Soins de longue durée

Programmes publics de
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September 25, 2007

Jim Keon
President
Canadian Generic Pharmaceutical Association
4120 Yonge Street
Toronto, ON M2P 2B8

Dear Mr. Keon:

Re: Submission Requirements for Generic Drug Products

I am writing to clarify the ministry's position regarding the submission requirements for an interchangeable product proposed to be listed in the Ontario Drug Benefit Formulary/Comparative Drug Index (the "Formulary"). This information is intended to provide the manufacturers with transparent and clear details about the drug submission process, and to minimize any potential confusion.

We intend to write to each manufacturer, however, we kindly request that you share this document with your member companies in the meantime. Please be advised that this document is not intended to provide a full and comprehensive outline of submission requirements. The manufacturer must refer to the applicable legislation, and the *Ontario Guidelines for Drug Submission and Evaluation* (the "Guidelines") for full details. Please note that the ministry will be updating the Guidelines to be consistent with the current statutory requirements, and all submission components highlighted below will be included. Until such time as the Guidelines are amended, please have reference to the legislative, regulatory and requirements as set out in this letter.

Firstly, effective as of November 1, 2007, please be advised that if any of the submission documents or materials are found to be deficient, the submission request for the proposed listing of the interchangeable product on the Formulary will automatically be deemed incomplete. If a submission is incomplete, the manufacturer must wait until the following monthly new submission date 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.

Notwithstanding the foregoing, there are two specific instances in which the manufacturer may be granted up to forty-eight (48) hours notice to correct its deficiencies for its submission to be deemed complete:

- where a manufacturer fails to provide an approved product monograph with a control number that matches the Notice of Compliance; and
- where a manufacturer provides a consent letter that fails to follow the appropriate format as indicated by the ministry.

The ministry will notify the manufacturer who, in turn, will have up to forty-eight (48) hours to perfect the submission. The notice from the ministry will clearly indicate the deadline by which the manufacturer must respond and provide the required document or information. If the manufacturer fails to respond within the permitted timeframe, the submission will be deemed incomplete and the submission will be held over until the following monthly submission review cycle.

Please note that the forty-eight (48) hours notice is not applicable for any other types of deficiencies.

A submission for an interchangeable product must meet the regulatory requirements as prescribed in Regulation 935 made under the *Drug Interchangeability and Dispensing Fee Act* (the "DIDFA Regulation"). Additionally, a submission must also include all applicable supporting documentation in order to be deemed complete.

Furthermore, any negotiations around pricing, utilization, monitoring and/or clinical research requirements must be complete. These general requirements apply to all multiple source drug products that are screened internally (i.e., streamlined generic submissions), and to all single source and non-streamlined multiple source drug products that have received a positive recommendation for listing from the Committee to Evaluate Drugs (CED).

Once this process is completed by the indicated deadlines (see part 12 below), including the ratification of the minutes from the CED meeting and product negotiations with the ministry, the submission will be considered complete. All recommendations will be submitted to the Executive Officer and are subject to the Executive Officer's review and decisions for inclusion in the next monthly Formulary Update.

Required Submission Components

Please find below some of the submission components in respect of which the ministry has received numerous inquiries.

1. Submitted Cover Letter

The manufacturer must provide a cover letter for each submission in which the manufacturer must, in addition to the standard requirements:

- Provide the product name, generic name, strength, dosage form and package format, as required.
- Identify the type of submission proposed for review (i.e. Ontario Drug Benefit (ODB), off-formulary interchangeability (OFI), etc.).
- Provide the name of the reference product for the determination of interchangeability.

- For interchangeable products where Health Canada has made a declaration of equivalence 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 (see part 5 below).
- Where the product name or the name of the manufacturer of the reference product is different from the original Canadian Reference Product, provide evidence to demonstrate the linkage between the different reference products.
- Provide evidence of bioequivalence where different dosage forms are submitted for the interchangeable drug product.
- Indicate if there are any business agreements or arrangements with any third party (e.g., consultant, cross-licensed, co-marketing, etc.) if applicable.

2. Third Party Involvement

Please note that in the event a third party is involved with the submission of the interchangeable product, the ministry will require a letter from both the manufacturer and the third party confirming this business arrangement.

In addition, the ministry will require a copy of the NOC from all parties involved in the submission.

3. 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 - Brand name/ generic name, strength, dosage (“the Product”) manufacturer by NOC holder (“the Manufacturer”) and signed by NOC holder.

Subject: NOC holder - Brand name/ generic name, strength, dosage (“the Product”) manufacturer by Other Party (“the Manufacturer”) and signed by Other Party.

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

<http://www.health.gov.on.ca/english/providers/pub/drugs/dsguide/dsguide_mn.htm>

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

4. Letter of Consent

The manufacturer must provide a letter of consent, which authorizes the ministry to collect, use and disclose the drug product information from the persons listed in clause 6(1)(b) of the DIDFA Regulation. The manufacturer must not include any restriction or limitations on this consent.

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

<http://www.health.gov.on.ca/english/providers/pub/drugs/dsguide/dsguide_mn.htm>

The letter template 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”)]

Please be advised that if a third party is involved in the filing of a submission, a letter is required from all of the parties which may have information regarding the product on file with Health Canada. The following format should be followed:

Subject: NOC holder -Brand name/generic name, strength, dosage form (the “Product”) manufactured by NOC holder. (the “Manufacturer”)

Subject: Other Party -Brand name/generic name, strength, dosage form (the “Product”) manufactured by Other Party (the “Manufacturer”)

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

5. Non Canadian Reference Products

In the event that the manufacturer submits evidence that Health Canada has made a declaration of equivalence on the NOC using a Non Canadian Reference Product (NCRP), the following requirements must be met:

a) Solid Oral Dosage Forms

1. If the NOC has a declaration of equivalence from Health Canada to a NCRP that has the SAME product name and SAME manufacturer as the Canadian reference product:
 - i. The manufacturer must indicate that a NCRP was used and provide justification in the cover letter as to why the NCRP was used.
2. If the NOC has declaration of equivalence from Health Canada to a NCRP that has a DIFFERENT product name or DIFFERENT manufacturer as the Canadian reference product:
 - i. The manufacturer must submit the dissolution profile data, as required by Health Canada for NCRPs, between the reference products.
 - ii. The manufacturer must indicate that a NCRP was used and provide justification in the cover letter as to why the NCRP was used.

b) Aqueous Solutions

1. For aqueous solutions, as classified under the *Health Canada Guidance for Industry: Pharmaceutical Quality of Aqueous Solutions*, the manufacturer must submit the following evidence:

- i. A waiver of comparative bioavailability studies for oral solutions, as applicable
- ii. A waiver of the requirement to demonstrate in vivo bioequivalence for aqueous solutions
- iii. Proof of purchase of Canadian reference product.
- iv. 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 information includes product name, strength dosage form and package format (if applicable) and the expiry date of the test and reference product.
- v. Any device attributes, as required by Health Canada
- vi. The manufacturer must indicate that a NCRP was used and provide justification in the cover letter as to why the NCRP was used.

c) Other Dosage Forms

1. For all other dosage forms, the manufacturer must submit the following evidence:
 - i. A comparative clinical /bioequivalence study and physiochemical study as required by Health Canada for NCRPs, between the reference products.
 - ii. The manufacturer must indicate that a NCRP was used and provide justification in the cover letter as to why the NCRP was used.

Please note that the ministry may ask for further documentation if there is insufficient linkage between the reference products.

6. Streamlined aqueous solutions

Please be advised that the exemption provided in subsection 6(5.1) of the DIDFA Regulation only applies to a drug product with a NOC issued on or after February 15, 2005.

7. Control Number

A manufacturer must submit a Product Monograph matching the control number on the original NOC issued by Health Canada. In the event that the control number differs, the manufacturer must clearly identify and clarify the different control number with respect to the Product Monograph (PM), NOC, Drug Notification Form (DNF), and the Certified Product Identification Document (CPID). In the case where the control number differs from the NOC, the manufacturer must also provide additional evidence that Health Canada has approved this 'other' control number with respect to its specific case, e.g., Letter of No Objection, Supplemental NOC, etc.

8. Master Formula or Certified Product Identification Document

The NOC for a generic drug product may contain approval for multiple strengths although the bioequivalence study with the original product may have been done on only one of the strengths. In cases where there is declaration of equivalence to the original 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 prove formulation proportionality among the various strengths.

A manufacturer must submit the CPID in order to satisfy the exemption for the master formulation 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 be advised that failure to provide either the master formulation or CPID will result in the submission being deemed as incomplete.

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 summary table of the list of ingredients used to manufacture a drug product as the official document for master formulation.

9. Proposed Drug Benefit Price

The regulations under the *Ontario Drug Benefit Act* (ODBA) and the DIDFA Regulation set the prices of interchangeable generic products at no more than 50 percent of the original product price. This applies to currently listed products and new additions to the Formulary.

The original product price is the price at the point in time in the Formulary when the interchangeable drug product is listed. The only exception to this would be where an original product was delisted. In this case, the reference product price is the price immediately before the original product was delisted.

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.) Please be advised that for listing purposes, the DBP must be expressed to four decimal places (\$0.0000).

If the manufacturer is not in agreement with the above price and is of the opinion that the submission meets the exemptions as stated in the regulations, please submit a written response by fax (416-325-6647) to the Executive Officer's attention stating the reasons for the exemption. All requests with respect to pricing negotiations must be sent directly to:

Ms. Helen Stevenson, Executive Officer
Ontario Public Drug Programs
Ministry of Health and Long-Term Care
415 Yonge Street, Suite 1601
Toronto, ON M5B 2E7

While there are no specific guidelines concerning the conditions under which the Executive Officer may consider an exemption, I can provide the following direction. In reviewing the proposed price for an interchangeable product the Executive Officer may consider an exemption,

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.

Please note that even if the manufacturer meets the exemption requirement, the Executive Officer is not required to negotiate DBP higher than at 50 percent of the original product price. As you may be aware, where the Executive Officer and the manufacturer cannot agree as to the DBP, the regulations require the Executive Officer to not list the proposed drug product.

10. Certification re 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. To satisfy this requirement, the manufacturer must submit a confirmation letter without any restrictions or limitations. The letter template 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")].

Please note that the Ministry may request for additional documentation to evidence 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.

11. Certification re "No Rebates"

Please be aware that, as a result of regulatory amendments, the manufacturer must certify by letter that no rebates were provided to persons listed under subsection 12.1(1) of the *Drug Interchangeability and Dispensing Fee Act* with respect to the drug product from the time that Health Canada approved the product for sale in Canada.

12. Declaration of Current Patent Status

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

- a signed statement from the manufacturer stating that the submitted product, to its knowledge, does not infringe any patents
- number and expiry date(s) of all Canadian patent(s)

13. Policy on Receipt of Submission

Please be advised that the Ontario Public Drug Programs operates from two different locations. All submissions and any additional related information must be addressed to:

Ms. Mona Sabharwal, Senior Manager
Drug Benefits Management
Ontario Public Drug Programs

Ministry of Health and Long-Term Care
3rd Floor, 5700 Yonge St.
Toronto, ON M2M 4K5

The manufacturer must submit two (2) copies for each multiple source product submission. If a manufacturer submits additional information, two (2) copies must also be provided. A submission will be deemed incomplete if this requirement is not met.

The ministry will **not accept faxed submissions or in electronic format**. All submissions must be delivered by either courier services or in person by the manufacturer to the address indicated above.

There will only be **one opportunity per cycle** for a manufacturer to make a complete submission for a streamlined multiple source product submission. Please refer to the ministry's website at http://www.health.gov.on.ca/english/providers/program/drugs/msp_update.html for the new submissions date and cut-off dates. For streamlined multiple source product submissions, the completed submissions must be received by the ministry staff at the above address before the 3:30 p.m. deadline as indicated on the ministry's website. Please be advised that the onus is on the manufacturer to check the ministry Bulletin Board System and the ministry's website for the most up-to-date information.

If the ministry receives any additional information past the deadline, then the additional information will only be screened and considered in the next month's review cycle.

Any submission request sent to an alternate address will not be processed.

14. Notification of Change

A manufacturer must report any and all changes 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. This may include, but not limited to, the following:

- **Changes to Product Monograph:** The ministry requires the manufacturer to explain the nature of the change(s) in the product monograph, and identify where this can be found in its submission. Please note that the ministry will not accept an annotated product monograph as the supporting document. Manufacturers are advised to provide a list describing in detail the revisions that were performed and where the revisions can be found in the revised product monograph. Evidence of Health Canada's approval may take the form of a NOC or No Objection Letter. If a Drug Notification Form (DNF) was issued, it should be submitted as well, otherwise, the manufacturer must provide a reason as to why a DNF was not submitted (e.g., Health Canada did not issue a DNF for our change).
- **Changes in the DIN, Ownership or Product Name:** A DNF and a NOC are required as evidence of Health Canada's approval. A failure to provide any of these documents will result in the submission being deemed incomplete. A No Objection Letter may substitute for a NOC.

Please be aware that any time a change is made to the drug product, the manufacturer must clearly identify the change, provide the rationale for the change, and submit the appropriate documentation.

When all regulatory and supporting document requirements are satisfied, a submission will be deemed complete and will enter the next stage of the review process.

With respect to off-formulary interchangeability submission requirements, we refer you to the OFI Guidelines, which were published on the ministry's website on March 2007. The OFI Guidelines can be accessed at:

http://www.health.gov.on.ca/english/providers/program/drugs/off_formulary_interchangeability.html

Should you wish to discuss further, please do not hesitate to contact me or Brent Fraser.

Sincerely,

- original signed -

Helen Stevenson
Assistant Deputy Minister and Executive Officer

cc. Brent Fraser, Director, Ontario Public Drug Programs
Mona Sabharwal, Senior Manager, Ontario Public Drug Programs