Ontario

Ministry of Health

OHIP, Pharmaceuticals and Devices Division

Ontario Guidelines for Diabetic Testing Agents

Submission Requirements and Review Process

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Introduction

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

The *Ontario Drug Benefit Act* (the "ODBA") defines "listed substance" to mean a substance, other than a drug, designated as a listed substance in the Formulary by the Executive Officer of the Ontario Public Drug Programs (the "Executive Officer"). Diabetic test strips are listed substances reimbursed for ODB-eligible persons in certain circumstances. The Executive Officer does not consider funding for diabetic test strips under the EAP.

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 designation as a listed substance on the Formulary.

Objective

The objective of this document is to provide guidance on submission requirements and the ministry's review process. The Guidelines are to be used in the preparation of a diabetic test strips submission provided to the Ministry of Health (ministry). The manufacturers, or those filing submissions on their behalf, are responsible for ensuring that all diabetic test strips submissions filed with the ministry contain sufficient information to satisfy the applicable requirements of the legislation and the Guidelines.

1. Checklists for Preparing Submissions

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

Requirement:	Included
Signed cover letter	☐
Table of contents	☐
Health Canada Documentation: Medical Device Licence; AND Medical Device Establishment Licence	 ☐ ☐
Letter of Consent	☐
Proposed Price Manufacturer list price; AND Pharmacy acquisition price	 ☐ ☐
Ability to Supply Letter	☐
Certification of Providing No Rebates Letter	☐
Evidence of product's safety and effectiveness	☐
Specifications for the finished product	☐
A copy of instructions	☐
A copy of the label	☐
ODB Financial Impact Analysis	☐

2. Submission Requirements for Diabetic Testing Agents

2.1 Cover Letter and Table of Contents

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

- The name of the diabetic test strips, chemical name, strength, and dosage form (including the various package sizes).
- Whether the manufacturer has any business agreements with any third party (e.g. consultant, cross-licensed, co-marketing, etc.) with respect to the diabetic testing agent, and, if so, the name of the third party / third parties. See additional information in section 7.1 of these Guidelines.

2.2 Evidence of approval from Heatlh Canada, including:

- A copy of the Medical Device Licence; and
- A copy of the Medical Device Establishment Licence.

2.3 Letter of Consent

A letter authorizing the Executive Officer to gain access to all information with respect to the diabetic testing agent in the possession of Health 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 diabetic testing agent in the possession of the Ministry to Health Canada, the government of a province or territory in Canada or the Canadian Agency for Drugs and Technologies in Health.

See Template Letter of Consent in section 6 below.

2.4 Proposed Price

Submit the following two prices:

- 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).

- 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 for any designation on the Formulary. If the price is accepted by the ministry and listed on the Formulary, it will apply to all pack sizes of the product.

2.5 Evidence Confirming Ability to Supply

Confirmation that the manufacturer is able to supply the diabetic testing agent at the proposed list price in a quantity sufficient to meet the anticipated demand for the product.

See Template Letter of Ability to Supply in section 6 below.

2.6 Certification Confirming That No Rebates Were Provided

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

See Template Letter Certification of Providing No Rebate in section 6 below.

2.7 Specifications for the finished product

2.8 A copy of instructions (patient package inserts, prescriber information, insert for the therapeutic use of the product)

2.9 A copy of the label of the finished product as it is intended to be sold in Canada

2.10 Financial Impact Analysis

ODB market share penetration or impact analysis on ODB expenditure, including the underlying assumptions for the calculations.

2.11 Evidence of Safety and Effectiveness

The following data to support the product's precision, accuracy, variability and reliability must be provided:

2.11.1 Within day performance

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.

2.11.2 Between day performance

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.

2.11.3 Environmental testing (Effect of varying temperature)

Effect of varying temperature (minimum of one low temperature (5°-10°C), room temperature (20°-25°C) and one elevated temperature (35°-45°C).

- 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 must 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 must 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.

- Individual deviations must be determined based on a standard glucose analyzer (YSI) result. Deviations must be segregated by environment temperature and/or humidity.

- Results must be presented at each environmental condition. Results at one concentration cannot be pooled across environmental conditions.

Furthermore, it is preferable that data be presented in an error grid although a deviation plot is acceptable.

- 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.

2.11.4 Environmental testing (Effect of varying humidity)

Effect of varying humidity (minimum of one low humidity (10%), one mid-range humidity (25% - 75%) and one high humidity (90%).

- 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 must 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 must 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.

- Individual deviations must be determined based on a standard glucose analyzer (YSI) result. Deviations must be segregated by environment temperature and/or humidity.

- Results must be presented at each environmental condition. Results at one concentration cannot be pooled across environmental conditions. Furthermore, it is preferable that data be presented in an error grid although a deviation plot is acceptable.

- 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.

2.11.5 Oxygen sensitivity testing

Testing at a partial pressure of oxygen equivalent to sea level and 10,000 ft or higher.

- Test conditions at sea level and 10,000 ft represent the minimum required test conditions. At each altitude a variety of glucose concentrations must 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 must 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.

- Individual deviations must be determined based on a standard glucose analyzer (YSI) result. Deviations must be segregated by altitude.
- Results must be presented at each altitude. Results at one concentration cannot be pooled across altitudes. Furthermore, it is preferable that data be presented in an error grid although a deviation plot is acceptable.
- 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.

2.11.6 Comparison of accuracy against a standard glucose analyzer (YSI)

- At least 200 reagent system units, from at least 10 vials or packages, shall be used.
- The ISO guideline for clinical accuracy (ISO 15197) should 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

Required Percentage of Samples in Specified Concentration Range	Glucose concentration mmol/L (mg/dL)
5	< 2.8 (< 50)
15	2.8 to 4.3 (50 to 80)
20	4.4 to 6.7 (80 to 120)
30	6.7 to 11.1 (120 to 200)
15	11.2 to 16.6 (201 to 300)
10	16.7 to 22.2 (301 to 400)
5	> 22.2 (> 400)

- 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.

- 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.

2.11.7 Interference testing

Interference testing with at least 15 chemicals which could potentially interfere on the basis of strip chemistry and monitor technology.

- 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.

- Submissions must include tests for compounds which test the specificity of the test strip and its accuracy with high, clinically achievable concentrations for each interfering compound.

- 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.

- 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 must be provided.

- 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.

2.11.8 Hematocrit testing

Hematocrit testing (minimum of five hematocrit levels tested from a low of at least 20% to a high of 60% or greater).

- 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.

- At each hematocrit level a variety of glucose concentrations must 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 must 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.

- Individual deviations must be determined based on a standard glucose analyzer (YSI) result. Deviations must be segregated by hematocrit levels.

- Results must be presented at each hematocrit level. Results at one concentration cannot be pooled across hematocrit levels. Furthermore, it is preferable that data be presented in an error grid although a deviation plot is acceptable.

- 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.

2.11.9 Human Factor Study and Consumer Study Field Testing

- Submissions must follow the ISO protocol and at least 50 subjects are to be included for each lot tested.

- 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.

2.11.10 Sample volume

Sample volume (accuracy of glucose concentrations with varying sample volumes).

- Submissions must 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.

- Individual deviations must be determined based on a standard glucose analyzer (YSI) result.
- Results must be presented for each volume tested. It is preferable that data be presented in an error grid although a deviation plot is acceptable.
- 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.

2.11.11 Dynamic Range, Linearity for glucose

- Submissions must 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.
- Test concentrations must cover the operating range of the meter and test strip.
- Individual deviations must be determined based on a standard glucose analyzer (YSI) result.
- Regression statistics must be presented and must evaluate slope, and intercept as well as the change in deviation with concentration based on a standard glucose analyzer's (YSI) result.

2.11.12 Stability test results included in the Health Canada Device review

2.11.13 Sensor movement testing results included in the Health Canada Device review

Note: Where applicable, raw data and a quantification of deviations between individual samples should be provided. Reporting only the mean deviation is not acceptable.

3. Submission Review Process

3.1 Filing of Submissions

A manufacturer who wishes to have a diabetic test strip considered for designation as a listed substance on the Formulary must file a submission with the ministry.

3.2 Written/Verbal Communication

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

3.3 Submission Receipt and Review

Diabetic test strips submissions are screened for compliance with applicable requirements in the legislation and these Guidelines by ministry staff in sequence, according to the date and time of receipt.

The targeted time frame for screening is approximately three weeks from the date the submission is received by the ministry.

Only products that are the subject of complete submissions (i.e. those that meet all applicable requirements) are eligible for review and consideration for designation as listed substances on the Formulary. The date that the ministry deems a submission complete, as well as the type of review (i.e. first review or reconsideration), determines the subsequent priority of the review of the product. The complete submission date refers to the date when the Notice of Drug Submission Status (NDSS) letter is sent.

3.4 Ministry Communication

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

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

3.5 Manufacturer's Response

A manufacturer must make reference to the diabetic test strip (product name/chemical name/strength/dosage form/package format and size), the master file number and the diabetic test strip file number(s) in all subsequent correspondence to the ministry. If a manufacturer receives an NDSS, which indicates that the submission was deemed incomplete, the manufacturer will be provided with 60 calendar days in which to provide the information required to complete the submission.

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

3.6 Review by the Advisory Committee

Complete submissions undergo review by the ministry's expert advisory committee, the Committee to Evaluate Drugs (CED). The complete submission is sent to a reviewer who reviews the submission and prepares a written report. Submissions are reviewed by the committee members and/or by other reviewers. The targeted time frame for the completion of reviews is four to six weeks. The CED and the ministry may require additional time to review complex submissions. Occasionally, a panel or subcommittee of the CED may be requested to review a specific submission, which will extend the timeline for the review.

3.7 Communication to Manufacturers

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

4. Format and Organization of Submissions

The OHIP, Pharmaceuticals and Devices Division accepts e-mail submissions. The submissions must be well organized and indexed/tabbed with description. Manufacturers must not provide submission information in one continuous document.

If the submission is too large to be sent by a single e-mail, the ministry will accept the whole submission via multiple e-mails. If the manufacturer is sending multiple e-mails for one submission, clearly identify that the e-mails belong to the same submission and how many total e-mails pertain to that particular submission.

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

5. Filing of Submissions

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

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

6. Templates and Checklists

Templates:

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

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

7. Additional Information

7.1 Third Party Involvement

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

7.2 Notification of Change

The ministry must be notified of the changes in ownership, licence, company name, labelling information, or other changes that may affect the quality or performance of the product.

7.3 Withdrawal Process

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

List of Abbreviations

BGTS	Blood Glucose Test Strip
CED	Committee to Evaluate Drugs
EAP	Exceptional Access Program
NDSS	Notice of Drug Submission Status
ODB	Ontario Drug Benefit
ODBA	Ontario Drug Benefit Act
OPDP	Ontario Public Drug Programs

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