Ontario

Ministry of Health

OHIP, Pharmaceuticals and Devices Division

# Ontario Guidelines for Nutrition Products

## Submission Requirements and Review Process

## Table of Contents

## Introduction

The Ontario Public Drug Programs (OPDP) provides funding for a number of publicly funded drug programs. The largest program is the Ontario Drug Benefit (ODB) program and 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"). Nutrition products are listed substances reimbursed for ODB-eligible persons in certain circumstances. The Executive Officer does not consider funding for nutrition products under the EAP. A manufacturer submitting a nutrition product for consideration for designation as a listed substance on the Formulary must provide a complete submission according to the Maximum Allowable Reimbursement (MAR) mechanism and pricing schedule, as well as the Guidelines.

## Objective

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

## 1. Checklist for Preparing Submissions

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

| Requirement | Included |
|---|---|
| Signed cover letter | ☐ |
| Table of contents | ☐ |
| Confirmation of the following:<br>• The product is not advertised in Ontario to the public.<br>• The distributor is located in Canada and does not rely on a direct sales network.<br>• The product is not intended for any of the following uses:<br>○ prescribed weight loss in the treatment of obesity<br>○ food allergies<br>○ body building<br>○ voluntary meal replacement<br>○ nutritional supplement<br>○ convenience<br>○ use as a replacement for breast feeding for infants with normal gastrointestinal absorptive function | ☐ |
| Nutrition Product Summary Sheet | ☐ |
| Nutrition Product Work Sheet | ☐ |
| Documentation with respect to complete ingredients, nutrient analysis of the product and the quantitative formula | ☐ |
| Daily volume to meet Recommended Nutrient Intake (RNI) | ☐ |
| A copy of the label | ☐ |
| Submitted Price | ☐ |
| Documentation regarding indications of use | ☐ |
| Product specific clinical studies | ☐ |
| Information demonstrating the benefit of the product in relation to the cost | ☐ |
| Letter of Consent | ☐ |
| Ability to Supply Letter | ☐ |
| Certification of Providing No Rebates Letter | ☐ |

# 2. Submission Requrements for Nutrition Products

## 2.1 Cover Letter and Table of Contents

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

- The name of the nutrition product, its active ingredient(s), strength(s), and dosage form(s) (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 nutrition product, and, if so, the name of the third party / third parties. See additional information in section 9.1 of these Guidelines.

## 2.2 Confirmation of the following:

- The product is not advertised in Ontario to the public.
- The distributor is located in Canada and does not rely on a direct sales network.
- 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.

## 2.3 Completed Nutrition Product Summary Sheet

See Template Nutrition Product Summary Sheet in section 8 below.

### 2.4 Completed Nutrition Product Work Sheet

See Template Nutrition Product Work Sheet in section 8 below.

Note**:** The Nutrition Product Worksheet was developed based on the guidelines that the Committee to Evaluate Drug's (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 external advisory committee's usual questions.

### 2.5 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)

### 2.6 Daily volume to meet Recommended Nutrient Intake (RNI)

### 2.7 Documentation with respect to the indications of use

### 2.8 Information demonstrating the benefit of the product in relation to the cost of the product and to any alternative products or treatments (if available)

### 2.9 A copy of the finished label of the product as sold in Canada

### 2.10 Submit a proposed drug benefit price for the product:

- 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).
- 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.

Where it is expected that patients would be required to pay a portion in addition to the applicable ODB program co-payment (i.e. the submitted price with mark-up is above the current MAR limit), please provide the amount that patients would be required to pay to four decimal places and a justification for this incremental cost.

### 2.11 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 8 below.

### 2.12 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 8 below.

### 2.13 Certification Confirming That No Rebates Were Provided

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

See Template Letter Certification of Providing No Rebate in section 8 below.

### 2.14 Product specific clinical studies

The manufacturer is required to provide product specific clinical studies (published or unpublished), and other clinical evidence demonstrating the product's therapeutic effectiveness, efficacy, and safety, including any information that relates to adverse reactions.

Comparative studies evaluating the product's therapeutic effectiveness, efficacy, and safety against other products or treatments are of particular interest.

**Note:** The *suggested* clinical requirements below are meant to provide assistance to manufacturers on how to conduct the study.

- The studies do not need to be Canadian but must be generalizable to the Canadian population.
- 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.
- Clinical trial should be conducted with patients who need the product.
    - The trial can be open label.
    - At least 25 subjects would need to be included, but depending on the difference expected, the number of subjects required can be calculated.
    - Patient selection is important.
        1. Researcher should decide the inclusion/exclusion criteria well before admitting patients to the study, taking into account:
            a. Patients for which the product is indicated; and
            b. Similarities amongst patients with respect to disease states and confounding factors.
        2. Reasonable chance of survival for the study and disease states that would allow the effect of nutrition to be assessed.
        3. 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.
    - Dose should be standardized to body mass index (BMI), or similar indices (e.g. ideal BMI, target BMI).

- Duration of treatment (2 to 3 weeks) should be sufficient to be able to observe an effect of the nutrition.
- The outcome measures of the study may vary according to the feed type. Primary outcome should be specified, and rationale provided. For example, 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.
- Comparator used should be the standard of care, that is, the comparator should be another nutrition 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.
- 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.
- Adverse events — Sufficient evidence of safety and tolerability should be measured and provided as well.

- The formulation composition of the test products.

### 2.15 Supplemental Data *(Optional)*

The manufacturer is encouraged to provide additional data, including post marketing safety reports, consumer feedback data and clinical practice guidelines to support comprehensive review of the nutrition product's therapeutic effectiveness and safety profile. Patient populations in studies and clinical evidence must be similar to the indicated patient population which will be served by the ODB formulary.

## 3. Requirements for Line Extension Submissions

A manufacturer requesting a change in the existing listed package size, or requesting listing for additional package format for a listed nutrition product, must provide the following:

- Detailed explanation of the change.
- Justification of the new pack size or package format.
- Confirmation that the change will not impact clinical response or product safety. If the change(s) will impact clinical response or product safety, include the supporting information/or/study listed for the Nutrition Product Work Sheet.
- Stability study test data to demonstrate the new product format is of suitable performance and quality to support an acceptable shelf life.
- A copy of the stability study protocol/design for all pack sizes of new formats.
- A copy of the product label for sale in the Canadian market.
- A copy of the new Nutrition Product Worksheet, and the supporting information or study listed in the Work Sheet is required.

Note: 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.

## 4. Submission Review Process

### 4.1 Filing of Nutrition Product Submissions

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

### 4.2 Written/Verbal Communication

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

### 4.3 Submission Receipt and Review

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

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 substancese 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.

### 4.4 Ministry Communication

Once a submission is screened by the ministry, an NDSS is issued to the manufacturer. Each submission is assigned a unique master file number, and each individual nutrition product within the same submission is assigned a unique nutrition 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.

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.

### 4.5 Manufacturer's Response

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

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

### 4.6 Review by the Advisory Committee

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

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

### 4.7 Communication to Manufacturers

A 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.

## 5. Notification of Change Submissions

The ministry must be notified of the changes in classification under the *Food and Drug Regulations* (Canada), ownership, nutrition product name, and changes in advertising policy.

All notification of change submissions must include a cover letter with the following:

- A description of the change(s) and a brief rationale for the change(s).
- The product(s) affected by the change(s).
- A copy of the product label for sale in the Canadian market, if applicable.
- Confirmation that formulation has not changed, and confirmation that the change will not impact clinical response or product safety.

Note: If formulation has changed i.e. the product efficacy, tolerance and/or safety are altered, the ministry requires the old and new quantitative formula, and nutrient formulation with the differences highlighted.

The ministry requires product specific clinical studies for the new formulation if the manufacturers have not provided satisfactory evidence to demonstrate that the product efficacy, tolerance and/or safety are not altered. A new Nutrition Product Work sheet and the supporting information or study listed in the Work Sheet is required, as applicable.

## 6. 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.

## 7. 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

## 8. Templates and Checklists

Templates, Summary Sheet and Work Sheet

- Template Letter of Consent
- Template Letter Confirming Ability to Supply
- Template Letter Certification of Providing No Rebate
- Nutrition Product Summary Sheet
- Nutrition Product Work Sheet

The ministry's Templates 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.

## 9. Additional Information

### 9.1 Third Party Involvement

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

### 9.2 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.

## 10. 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.

| | |
|---|---|
| 1.Lactose Free | Lactose free |
| 2. Lactose Containing | Contains lactose |
| 3. Fibre Containing | Lactose free<br>Added fibre or naturally occurring fibre |
| 4. High Protein Nitrogen | Lactose free<br>Protein greater than 20 – 25% of calories and/or a calorie:nitrogen ration of 125:1 or less. |

### 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.

| | |
|---|---|
| 1. Protein | Only contains protein |
| 2. Carbohydrate | Only contains carbohydrate |
| 3. Fat | Only contains fat |

### D. Chemically Defined Formula

| | |
|---|---|
| Oligomeric Solutions<br>(Other names: Semi-elemental; Chemically Defined) | Solutions containing peptides and amino acids.<br>No lactose or minimal lactose<br>No fibre |
| Monomeric Solutions<br>(Other names: Elemental; Chemically Defined) | Solutions containing amino acids as the protein source<br>No lactose<br>No fibre |

### 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, 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.

| | |
|---|---|
| 1. Lactose Free | Lactose free |
| 2. Fibre Containing | Lactose free<br>Added fibre or naturally occurring fibre |

### 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

| | |
|---|---|
| Oligomeric Solutions<br>(Other names: Semi-elemental; Chemically Defined) | Solutions containing peptides and amino acids<br>No lactose or minimal lactose<br>No fibre |
| Monomeric Solutions<br>(Other names: Elemental; Chemically Defined) | Solutions containing amino acids as the protein source<br>No lactose<br>No fibre |

### H. Pediatric Formula -Others

These are nutrition products other than those already described above.

## List of Abbreviations

| | |
|---|---|
| BMI | Body Mass Index |
| CED | Committee to Evaluate Drugs |
| EAP | Exceptional Access Program |
| MAR | Maximum Allowable Reimbursement |
| NDSS | Notice of Drug Submission Status |
| ODB | Ontario Drug Benefit |
| ODBA | Ontario Drug Benefit Act |
| OPDP | Ontario Public Drug Programs |
| RNI | Recommended Nutrient Intake |

This page intentionally left blank