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GUIDANCE DOCUMENT

Product Monograph

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Health Products and Food Branch

Canada 

<p>Our mission is to help the people of Canada maintain and improve their health.</p> <p style="text-align: right;"><i>Health Canada</i></p>	<p>The Health Products and Food Branch (HPFB)'s mandate is to take an integrated approach to managing the health-related risks and benefits of health products and food by:</p> <ul style="list-style-type: none"> • Minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and, • Promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health. <p style="text-align: right;"><i>Health Products and Food Branch</i></p>
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Également disponible en français sous le titre : Ligne directrice : Monographie de produit

FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with the policies and governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are implemented in a fair, consistent and effective manner.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document **may be** acceptable provided they are supported by adequate scientific justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this guidance, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidances.

DOCUMENT REVISION HISTORY

Version	Document Name	Change Made	Dates
1	Guidance for Industry: Product Monograph	Initial Issuance of Guidance and Templates	Adopted Date 2003/09/22 Effective Date 2004/10/01
2	Guidance Document: Product Monograph	Overdosage section <ul style="list-style-type: none"> • Addition of standard boxed message Reporting Suspected Side Effects <ul style="list-style-type: none"> • Administrative updates 	Effective Date 2010/01/01
3	Guidance Document: Product Monograph	Part III: Patient Medication Information (PMI) <ul style="list-style-type: none"> • Part III, formerly titled ‘Consumer Information’ was revised to include plain language elements, including new language and formatting 	Adopted Date 2013/09/12 Effective Date 2014/06/01
4	Guidance Document: Product Monograph	Part I: Health Professional Information Part II: Scientific Information Appendices A, B, C, D All 5 associated templates <ul style="list-style-type: none"> • These sections were revised with plain language enhancements including reorganization of information 	Adopted Date 2016/06/17 Revised Date 2016/12/09 Effective Date 2017/06/09

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1 INTRODUCTION

1.1 Purpose

The purpose of this guidance document is to assist sponsors in developing product monographs with acceptable format and content. The product monograph is an integral part of New Drug, Supplement to a New Drug, Abbreviated New Drug and Supplement to an Abbreviated New Drug Submissions. A product monograph is intended to provide the necessary information for the safe and effective use of a new drug and also to serve as a standard against which all promotion and advertising of the drug can be compared.

1.2 What Is a Product Monograph?

A product monograph is a factual, scientific document on a drug product that, devoid of promotional material, describes the properties, claims, indications, and conditions of use for the drug, and that contains any other information that may be required for optimal, safe, and effective use of the drug. A product monograph should include appropriate information respecting the name of the drug, its therapeutic or pharmacologic classification, its actions and/or clinical pharmacology, and its indications. The product monograph should also include: contraindications, dosage and administration, symptoms and treatment of overdose, dosage forms, warnings, precautions, adverse reactions, drug interactions, effects on laboratory tests, storage and stability, special handling instructions, pharmaceutical information, information on clinical trials, microbiology, toxicology, and information for the patient. In addition, the product monograph should state both the dates of initial approval and revision.

1.3 Medical and Scientific Implications

From a medical and scientific standpoint, the prime objective of a product monograph is to provide essential information that may be required for the safe and effective use of a new drug.

As far as the health professional is concerned, the information provided should be as meaningful and helpful as possible. However, only those indications and clinical uses that are based on substantial evidence of efficacy and safety and that are the subject of a New Drug Submission, or an Abbreviated New Drug Submission, or a Supplement to either submission that has received a Notice of Compliance pursuant to Section C.08.004 of the *Food and Drug Regulations*, should be included in the product monograph. The product monograph is not intended to serve as a repository of all information currently available on a drug. The product monograph is based primarily on data submitted by a sponsor and evaluated by Health Canada as part of the regulatory drug review and authorization process. As a result, it may not reflect the entire existing body of evidence.

1.4 Regulatory Implications

1.4.1 Product Monograph

The product monograph, as a document, will be included by Health Canada as part of the Notice of Compliance respecting a New Drug Submission or, when appropriate, a Supplement to a New Drug Submission, an Abbreviated New Drug or a Supplement to an Abbreviated New Drug Submission.

The product monograph serves as a standard against which all promotional material, or advertising distributed or endorsed by the sponsor about the drug can be compared. The product monograph serves the following purposes:

- It contains all the representations to be made in respect of the new drug as required by paragraph C.08.002(2)(k) and C.08.003(2)(h) of the *Food and Drug Regulations*.
- It fulfils the requirements for adequate directions for use for new drugs included in a number of Sections having to do with labelling in Parts C and G of the *Food and Drug Regulations*.
- It identifies the information that is to be provided on request when a package insert is not included with a new drug product and a health professional requests information relevant to clinical use.
- It identifies the information that should be provided to the patient respecting the use of that product [that is (i.e.) Part III, Patient Medication Information].
- It establishes the limitations/parameters for all advertising, representations, and promotional or information material distributed or otherwise endorsed by the sponsor. Subsection C.08.002(2) of the *Food and Drug Regulations* prohibits the advertising of a new drug for any use of the drug or for any claim that has not been the subject of a cleared submission. As this information is represented in the product monograph, no professional or published literature should be quoted, distributed, or otherwise provided by the sponsor if it refers to claims or indications for use that are not supported by the current product monograph.

1.4.2 Prescribing Information

The information described in Part I (Health Professional Information) of the product monograph contains prescribing information, and serves the following purposes:

- It identifies the information to be provided if a package insert is included with a new drug product.

- It identifies information to be provided as part of all professional material and that may be used for promotional and advertising purposes, other than in the case of reminder notices.

In addition to Part I, the information described in Part III (Patient Medication Information) may also be provided as part of the package insert for a new drug product.

1.4.3 Patient Medication Information

The information described in Part III (Patient Medication Information) of the product monograph contains information for the patient. This portion of the product monograph identifies the information that is to be provided to the patient or consumer either at the time of dispensing as a separate document, or as a package leaflet.

1.5 When is a Product Monograph Required?

A draft copy of the proposed or revised product monograph should be included in the master volume when a New Drug, Supplement to a New Drug, Abbreviated New Drug or Supplement to an Abbreviated New Drug Submission is filed for either a prescription or nonprescription drug.

Health Canada will advise the sponsor if the New Drug Submission or Supplement to a New Drug Submission is judged to be incomplete in complying with the requirements of Section C.08.002 or C.08.003 of the *Food and Drug Regulations*.

1.6 Revisions

A product monograph can be revised by filing an acceptable Notifiable Change or Supplement to a New Drug Submission or Supplement to an Abbreviated New Drug Submission. Revisions should be initiated by the sponsor whenever significant updating of the product monograph is required in order to incorporate additions or other changes related to safety (particularly with respect to warnings, precautions, adverse reactions, and mode of administration) that may be necessary as a result of newly available information. The product monograph should also be revised whenever substantial information is available to support significant new indications or when other changes or deletions in the indications and conditions of use are required as a result of additional available information. In some instances, it may be necessary to inform the health professional or the patient about special hazards or to issue special warnings before there is an opportunity to revise the product monograph.

Pursuant to paragraph C.08.006(f) of the *Food and Drug Regulations*, Health Canada may request that the sponsor revise the product monograph if, on the basis of new information, it is considered to be false, misleading, or incomplete in any respect. Whenever periodic reports on a

new drug are requested pursuant to paragraph C.08.008(a) of the *Food and Drug Regulations*, the sponsor should determine whether significant changes should be made in the product monograph as a result of the additional information available.

1.7 Distribution

A copy of the most recently updated product monograph (including the Patient Medication Information) should be provided by the sponsor to health professionals whenever they request prescribing information or other information relevant to the clinical use of the new drug. For products that have received a Notice of Compliance (NOC) and are marketed, the product monograph must be available in both official languages.

The Health Professional Information portion of the product monograph may also be made available as a package insert. This portion should therefore be provided in connection with the promotion or advertisement of the drug or included in reference manuals distributed or endorsed by the sponsor. In addition the Patient Medication Information may also be provided as part of the package insert for a new drug product.

A copy of the most recently updated product monograph (including the Patient Medication Information) should be provided to health professionals prior to, or coincident with, the first direct promotion or marketing of a new drug, and to any health professionals to whom the sponsor sells a new drug before it is generally available.

Additional information may be found in Health Canada's *Guidance Document: Labelling of Pharmaceutical Drugs for Human Use*.

1.8 Inquiries

The Regulatory Project Management Division of the Therapeutic Products Directorate or the Office of Regulatory Affairs of the Biologics and Genetic Therapies Directorate may assist sponsors with questions concerning the filing of a draft product monograph. General inquiries may be directed to RPM_Division-GPR_Division@hc-sc.gc.ca or BGTD_ORA@hc-sc.gc.ca.

1.9 Guiding Principles

A product monograph should be prepared with the following guiding principles as a basis for the information:

- Avoid duplication of information. Wherever possible, information should only be presented once in the product monograph.
- Key information should be easy to locate.

- Information should be presented in a consistent format to facilitate ease of retrieval, particularly in an electronic environment. This requires the standardization of terminology and the inclusion of hyperlinks for searching.

1.10 Using the Guidance Document

The main part of this document is referred to as the "core document" and it provides guidance for preparing a standard product monograph. For other drugs that have specific information requirements, please consult the following appendices:

Notice of Compliance with Conditions (NOC/c)	Appendix A
Subsequent Entry Products (except for Schedule C and D products)	Appendix B
Schedule C Products	Appendix C
Schedule D Products	Appendix D

If more than one appendix applies to a product monograph (for example, a biologic that also has an NOC/c), the requirements from both need to be incorporated into the product monograph.

1.10.1 Template

A product monograph should be prepared in the same software format as the other submission documents. An electronic template (in Microsoft Word® format) for a standard monograph, as well as those listed above, is provided with this guidance document.

Instructions that may be useful in preparing the product monograph are contained within square brackets [...] and are to be removed by the sponsor during preparation.

Information to be included in the product monograph is contained within pointed brackets <...>.

2 PREPARING A STANDARD PRODUCT MONOGRAPH

Each product monograph will consist of three distinct parts:

Part I: ***Health Professional Information***

Contains information required for the safe and appropriate prescribing, dispensing and administering of the drug product.

Part II: Scientific Information

Contains more in-depth scientific/research information such as non-clinical toxicology and data from animal studies and human clinical trials. It complements and extends the information contained in Part I.

Part III: Patient Medication Information

Contains information derived from Parts I and II that helps the patient understand what the medication is, how to use it and what the potential side effects are. It is also intended to serve as a guide for health professionals to easily identify the information needed for counselling patients. It is presented in a language and format that is appropriate for a patient audience, including the general public. Part III is required for all drugs, regardless of the location of use [for example (e.g.), hospital] or method of administration (e.g., by a third party).

2.1 General Instructions

The guidance document presents the sections of the product monograph in the order that they should appear. Health Canada recognizes that this guidance document may not address the information requirements for all drugs and individual judgement remains critical in assessing how or whether to present the information. If a section is not included, a rationale should be provided by the sponsor.

- "Health professional" is the preferred term that should be used in Part I (Health Professional Information) and Part II (Scientific Information) of the product monograph when referring collectively to professionals. It is also intended to be used in place of singular terms such as: health care provider, health care practitioner, etcetera (etc.).
- For pharmaceutical prescription products and those administered or obtained through a health professional, the product monograph should be supplied to Health Canada in both official languages (i.e., Canadian English and French). Please refer to the *Guidance Document Questions and Answers: Plain Language Labelling Regulations* for more details regarding the timing of the submission of these documents.
- Suggested standard statements are provided for sponsors to use in the preparation of the product monograph. They are identified in the guidance document by the preceding instruction: "the following or similar statement". If a standard statement is applicable, the sponsor is required to use it. If a statement does not fit a particular product, the sponsor may amend it.
- Words or phrases that lack a commonly understood meaning (e.g., imprecise quantitative terms), are not easily defined, are vague, misleading, or promotional in tone should be avoided (e.g., unique, novel, convenient, potent).

2.2 Style Guide

- Paper: 21.6 x 27.9 centimetre (8½ x 11") portrait orientation
- Margins: 2.5 centimetre (1") top, bottom and sides
- Line spacing: single
- Font: Parts I, II and III: Sans Serif type fonts (e.g., Calibri 12 point, Arial 11 point)
Patient Medication Information leaflet: Sans Serif type fonts, text - 10 point, tables - 9 point.
- Justification: left
- Page numbers: on bottom right hand side
- Start each Part on a new page
- Heading format: see template
- When a cross-reference is included, a hyperlink should be built in.
- For Parts I and II, the first use of the brand name should be followed by the proper name (or common name, where there is no proper name) in final dosage form, in parentheses. In describing the drug's actions, pharmacology, and toxicology, the proper name (or common name, where there is no proper name) in final dosage form should be used.
- For Part III (Patient Medication Information), brand name should be used to describe the drug, or if there is no brand name, use the proper name of the drug in final dosage form. Where there is no proper name, use the common name in final dosage form.
- Upper case font and bold type face should be used for emphasis sparingly.
- Paragraph numbering should not be used.
- If abbreviations are used in a table, a legend should be included at the bottom of table.

Additional style instructions are provided for the Patient Medication Information (see Section 5.3).

2.3 Title Page

The title page should bear the following information in the following sequence:

- a) the words "Product Monograph, Including Patient Medication Information",
- b) the scheduling symbol (e.g., Pr, N, T/C), as applicable,
- c) the brand name of the drug product,
- d) the proper or common name of the drug product(s) in final dosage form,
- e) the strength(s), dosage form(s) and route(s) of administration,

-
- f) where there is no proper or common name for the drug product in final dosage form, list all medicinal ingredients by their proper or common name, along with the dosage form of the final drug product,
- g) the pharmaceutical standard of the drug product (e.g., prescribed, pharmacopeial or professed), if applicable,
- h) the therapeutic, diagnostic or pharmacological classification and code in accordance with the World Health Organization's Anatomical Therapeutic Chemical (ATC) index¹,
- i) the name, place of business and website of the sponsor, and, when appropriate, the name and place of business of the distributor in Canada,
- j) date: for a new product monograph use the date of initial approval. For subsequent revisions to any part of the product monograph, also include the most current revision date; and,
- k) the submission control number.

When the title page would normally be omitted (i.e., in package inserts or advertising copy) items *a* to *k* should be repeated on page 1 of the product monograph.

Presentation: see template

2.4 Recent Major Label Changes

List the section headings in the product monograph where any major label changes related to safety and efficacy have been made within the past 24 months, under the following sections:

- Serious Warnings and Precautions Box;
- Indications;
- Contraindications;
- Dosage and Administration;
- Warnings and Precautions;

Major label changes include Level I changes filed with a Supplement to a New Drug or Supplement to an Abbreviated New Drug Submission, or a Level II Notifiable Change for either a prescription or non-prescription drug. Criteria for determining the levels or types of changes are described in both the *Guidance Document: Post Notice of Compliance (NOC) Changes*:

¹ ATC/DDD Index 2014 (www.whocc.no/atc_ddd_index)

Safety and Efficacy Document and the Guidance Document: Post Notice of Compliance (NOC) Changes: Quality Document.

The headings of the changed sections (including subheadings where applicable) should be listed in the order in which they appear in the product monograph, on separate lines. The section numbers should be included as well, along with the dates the changes were authorized. Dates should be in the following format: (MON/YYYY). For example:

Warnings and Precautions, Pregnant Women (6.1.1) 12/2013

If there were multiple changes under the same heading or subheading within the past 24 months, only list the date of the newest change. If there were changes under more than one subheading within the same section during the last 24-month period, list each of these changes separately. For example:

Warnings and Precautions, Pregnant Women (6.1.1) 12/2013
Warnings and Precautions, Pediatrics (6.1.3) 09/2014

All major label changes made in the last 24 months should be indicated within the body of the product monograph where they occur, by a vertical line on the left edge of the page.

Presentation: list (see template)

2.5 Table of Contents

The product monograph should include a table of contents with page numbers. Section headings are standard and do not change; however, subsection headings should be included in the table of contents where applicable. All section and subsection headings should be numbered and hyperlinked to the corresponding area within the product monograph.

Presentation: see template

3 PART I: HEALTH PROFESSIONAL INFORMATION

3.1 Indications

The indications listed in this section should be based on substantial evidence of the drug product's efficacy and safety, derived from adequately designed and conducted clinical studies. Only those indications authorized by Health Canada can be included. An indication should specifically refer to the disease(s), medical condition(s) or prophylactic measure(s) the drug is authorized to treat or manage and include the patient population that the drug is intended to treat or manage (e.g., patients with atrial fibrillation, pediatrics).

Only those diagnostic test kits that have been licensed for sale by Health Canada can be named in this section. Any relevant information about the kit should be included in the Clinical Trials section.

Where applicable, a statement should be included to indicate that the drug product is intended for use as an adjunct to other forms of management of the condition (e.g., lifestyle modification in osteoporosis).

When appropriate, this section should also describe the optimal use of the drug and the limitations of usefulness.

When the genotype of the patient or that of an infectious agent will affect the treatment outcome, relevant information should also be included in this section.

Any special restrictions with respect to the use (e.g., specific health professionals) and/or distribution of the drug (e.g., a hospital setting, ambulance), which may be required on a temporary or permanent basis, should be declared in this section.

If there are situations where the use of this drug product is not therapeutically appropriate (e.g., maintenance versus acute therapy), this information should be included.

It is beyond the scope of the product monograph to provide information on the disease targeted by the indications.

Presentation: bullet list (for indications) and narrative.

3.1.1 Patient Subsets

3.1.1.1 Pediatrics

For indications authorized for adults in general, a statement regarding use in the pediatric population should be included. The term pediatric generally pertains to persons between birth and 18 years of age, but it is recognized that this may not apply to all drug products², therefore the Pediatric subtitle should include the age upon which the pediatric recommendation is based. For example, 12 years of age should be used if the clinical trials included only children up to the age of 12. If pediatric patients were included on the basis of criteria other than age (e.g., by weight, without a specified age range), this should be reflected here instead. One of the following or similar statements should be used:

² ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population, January 2001

Pediatrics (age range): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of [Brand name] in pediatric patients has been established; therefore, Health Canada has authorized an indication for pediatric use. [Include cross-reference to relevant sections.]

or

Pediatrics (age range): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

or

Pediatrics (age range): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of [Brand name] in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use. [Include cross-reference to relevant sections.]

Any information relating to clinical trials which support the Health Canada authorized indication(s) should be included in the Clinical Trials section of Part II: Scientific Information.

3.1.1.2 Geriatrics

For indications authorized for adults in general, a statement regarding use in the geriatric population may be included. The term geriatric generally pertains to persons over 65 years of age but it is recognized that this may not apply to all drug products, therefore, if applicable, the Geriatric subtitle should include the age upon which the geriatric recommendation is based. For example, 75 years of age would be used if the study data included only the frail elderly. One of the following or similar statements may be used:

Geriatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

or

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness.

3.2 Contraindications

This section should describe absolute contraindications, meaning those situations in which the drug should **not** be used because the risk outweighs **any** potential therapeutic benefit.

For contraindicated drug-drug or drug-food interactions a brief statement should be included here with a cross-reference to the detailed information in Drug Interactions.

For hypersensitivity reactions, the following or similar statement should be used:

<Proper name> is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.

Presentation: bullets

3.3 Serious Warnings and Precautions Box Location

In those cases where there is a Serious Warnings and Precautions Box, it is to be located immediately following the Contraindications section (for more information, see section 3.7 Warnings and Precautions).

3.4 Dosage and Administration

3.4.1 Dosing Considerations

This subsection should briefly list the safety issues to consider when developing a dosage regimen in an individual patient (e.g., renal disease, age, concomitant therapy, genetic polymorphism, titration). Where different dosage forms are available, if the dosages are not equivalent the conversion value should be stated (e.g., changing from intravenous to oral therapy where a ratio other than 1:1 exists).

Presentation: bullets

3.4.2 Recommended Dose and Dosage Adjustment

This subsection should provide detailed and practical information on the recommended dosage. The subsection should include: dosage schedules, the initial dose, the optimal method of titrating dosage, the dosage range, maximum daily dose, maintenance dosage, duration of treatment and drug discontinuance. When applicable, dosages should be provided for each indication, route of administration and dosage form.

Guidance should be given on the dosage adjustments necessary when administering the drug in special populations for whom the product is indicated (e.g., children, elderly) or in the presence of pathologies (e.g., renal disease, hepatic disease, genetic polymorphism). When an age descriptor is used (e.g., children, pediatrics), the age range

should be specified. In the absence of a Health Canada authorized pediatric indication, this subsection should emphasize that the product is not indicated in the pediatric population. The following or similar statement should be used:

Health Canada has not authorized an indication for pediatric use. [Include cross-reference to relevant sections, if applicable.]

If no dosage adjustments are required a statement to that effect should be included (e.g., No dosage adjustment required in hepatic or renal impairment).

Presentation: narrative

3.4.3 Administration

This subsection should include details concerning the methods of administration, particularly for parenteral products or for other unique formulations such as inhalation devices, implants, and transdermal formulations. Where aseptic techniques are required, this information should be included.

Use in combination with other drugs (e.g., in same intravenous solution) should also be described. Special considerations for administering the drug with respect to the formulation should be specified (e.g., do not crush; if capsule contents can be sprinkled; etc.). For parenteral products or those with other unique formulations, details of the administration technique for each route should be given, including use in infusion or lavages, etc.

The time of day for optimal drug effect should be indicated (e.g., evening, morning, etc.) where applicable. Timing of administration of a dose with respect to food should be indicated using the following or similar statements:

Empty stomach, 1 hour before or 2 hours after meals;

Before meals, usually 15 to 30 minutes before meals;

Empty stomach preferably, may be taken with food if gastric upset occurs;

With or without food, may be given without regard to meals;

Consistently with or without food as presence or absence of food may alter bioavailability.

Presentation: narrative and/or table

3.4.3.1 Reconstitution

Oral Solutions

This subsection, which is essential for all drug products that require reconstitution prior to patient administration, should list all recommended diluents for reconstitution. Directions for reconstitution should include the volume and type of diluents to be added and the approximate volume and concentration of the resulting product.

The recommended storage period and conditions for each solution should be stated (include cross-reference to Storage, Stability and Disposal).

Presentation: narrative and/or table

Parenteral Products

For parenteral drugs requiring reconstitution or dilution before use, it is recommended that the relevant information be presented in a table under subheadings of the recommended routes of administration. The recommended diluent for each proposed route of administration should be included under each subheading. A reconstitution table should include the following four columns:

- vial size;
- volume of diluent to be added to vial;
- approximate available volume;
- nominal concentration per millilitre.

For *intravenous* use, information should be separated for:

- direct intravenous injection;
- intermittent intravenous infusion; and
- continuous intravenous infusion.

Any specific precautions should be specified below the table. For infusions, all common intravenous infusion fluids with which the drug has been shown to be incompatible, and the method of preparing the dilutions, should be listed.

The recommended storage period and conditions for each preparation should be stated (include cross-reference to Storage, Stability and Disposal).

Presentation: table and narrative (see template).

3.4.4 Missed Dose

This subsection should provide guidance on the actions to be taken in the event that a patient misses a dose.

Presentation: narrative

3.5 Overdosage

This section should include the following:

- a description of the signs and symptoms of overdose;
- current recommended management of overdosage (e.g., antidotes and/or other clinical interventions required);
- the human lethal dose (if available), and the maximum dose reported with recovery, with or without residual damage; and
- procedures that, by experience with this or similar type drugs, are known or reasonably expected to be unnecessary or unsuitable (e.g., those that may be hazardous to the patient).

Presentation: narrative

The following boxed statement is to be added at the end of the Overdosage section:

For management of a suspected drug overdose, contact your regional poison control centre.

3.6 Dosage Forms, Strengths, Composition and Packaging

The following information should be included in a summary table at the beginning of this section:

- all authorized dosage forms, and strengths of each form in terms of the concentration of medicinal ingredient (e.g., suspension/50 mcg [micrograms] per metered spray)
- the recommended route of administration for each form
- where applicable, the composition (e.g., components making up the capsule shell, coating, patch, etc.) should also be included for each strength of each dosage form
- a qualitative, alphabetical listing of all non-medicinal ingredients.

The terminology for the routes and forms will be in accordance with those published by Health Canada.

Different strengths of the product containing identical ingredients should be grouped together whenever possible. Different strengths containing different ingredients should be listed on a separate line.

Presentation: table (see template)

A complete description of each authorized dosage form's physical characteristics should be provided, including identifiable markings. Other items such as those required for administration or quality control, reconstitution, elution etc. should also be included.

Other unique formulation information should be included in this section (e.g., inert components remain intact after elimination).

A description of the type and size of all authorized packaging formats should be included (e.g., "supplied in bottles of 100's, 500's, and 1,000's and in blister packs of 100's"). Any additional packaging information (e.g., latex), or potential for cross-contamination during manufacturing that may impact patient safety should be described (e.g., peanuts, gluten).

Presentation: narrative

3.7 Warnings and Precautions

This section contains information about all serious effects that may pose a hazard to the patient, as well as precautions to be exercised by the health professional or by the patient in order to ensure safe and effective use of the drug.

3.7.1 Serious Warnings and Precautions Box

Clinically significant or life-threatening safety hazards when taking the drug should be highlighted in the Serious Warnings and Precautions Box. Information for the Serious Warnings and Precautions Box may be drawn from any section of the product monograph and will be determined in consultation with Health Canada. Information related to clinically significant or life-threatening product class-related adverse reactions should also be included, if applicable, with a cross-reference to the Adverse Reaction section. If there are no serious warnings or precautions, this box is omitted.

A **brief statement** is provided in the Serious Warnings and Precautions Box with a cross-reference to the applicable section of the product monograph where complete details are provided. The text in the box should generally not exceed 20 lines.

Statement examples:

- Drug interactions with digoxin, phenytoin (see Drug Interactions section);
- Liver toxicity (see Hepatic section below);
- Should only be administered by health professionals experienced with cancer chemotherapeutic drugs (see Indications).

Information on products requiring administration by a specialized health professional or in a restricted setting, should also be highlighted in the Serious Warnings and Precautions Box (i.e., a brief statement) with a cross-reference to the more detailed information in the Indications section.

The Serious Warnings and Precautions box is to be located immediately following the Contraindications section. Include the following or similar statement in the Warnings and Precautions section:

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

Presentation: bullet form within a box (see template)

3.7.2 Specific Subheadings

Subheading should be used to group the information in this section. Subheadings should be alphabetically ordered as presented below, and only used where applicable. For a particular subheading, if there are no effects that may pose a hazard to the patient or precautions to be exercised by the health professional or patient in order to ensure safe and effective use of the drug, then the subheading should be omitted. Additional subheadings may also be used. Information presented within subheadings should be in decreasing order of importance.

General: This subsection contains information that does not fall under the subheadings listed below.

Carcinogenesis and Mutagenesis: This subheading should include only human data where there is evidence that the drug is carcinogenic or mutagenic. Where there is only animal data, a cross-reference to the animal data in the Non-clinical Toxicology section should be provided.

Cardiovascular

Dependence/Tolerance: This subheading should include effects resulting from both physical and psychological dependence. The amount of drug, duration of time taking the drug and characteristics of the dependence and withdrawal should be described. Treatment of the effects of the dependence should be provided.

Driving and Operating Machinery: This subheading should include any effects that may impair performance of a task requiring special attention, including driving and operating machinery, along with the following or similar statement:

Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Ear/Nose/Throat

Endocrine and Metabolism: This subheading should specify genetic polymorphism where applicable.

Gastrointestinal

Genitourinary

Hematologic

Hepatic/Biliary/Pancreatic: When possible, idiopathic versus metabolic liver failure should be described.

Immune: This subheading should include effects resulting from altered immune reactivity, clinically expressed as either immune activation or immune suppression. Immunogenicity or allergenicity should be given special consideration if applicable.

Monitoring and Laboratory Tests: This subsection should include important monitoring parameters (e.g., blood pressure), observations, laboratory or other tests required to monitor response to therapy and possible adverse reactions. The frequency of monitoring before, during and after therapy should be included. Information regarding the range of normal and abnormal values expected in a particular situation should be provided. Appropriate response to particular laboratory values should be included.

Neurologic

Ophthalmologic

Peri-Operative Considerations: This subsection should include information on management before, during and after surgery. Practical details on drug discontinuation or dosage adjustment should be provided.

Psychiatric: Behavioural changes (e.g., suicidal ideation) should be included in this subsection.

Renal

Respiratory

Sensitivity/Resistance

Sexual Health

Reproduction: Where applicable, include instructions for pregnancy prevention/contraception and information about Pregnancy Registries.

Function: Include effects on sexual desire, erection, orgasm and ejaculation.

Fertility: A summary of relevant information on effects of the drug on fertility from animal or human exposure should be included under this subheading. Where there is absence of information, clearly state that no data exist.

Skin: Where applicable, human photosensitivity (photoallergic or phototoxic) reactions should be included. Where there is only non-clinical data, a cross-reference to the Non-clinical Toxicology section should be provided.

Special Populations

Pregnant Women: The type of data should be briefly stated (human or animal) and the recommendation (e.g., avoid in a particular trimester) for prescribing the drug safely should be given.

Teratogenic and nonteratogenic effects on the fetus should be included (e.g., withdrawal symptoms, hypoglycemia). If contraindicated in pregnancy, this should be included in this subsection and the Contraindications section. Include the following information, when available:

- Disease-associated maternal and/or embryo/fetal risk
- Maternal adverse reactions
- Fetal/Neonatal adverse reactions
- Labour or delivery

Include a cross-reference to the Dosage and Administration section when there are dose adjustments during pregnancy and the postpartum period.

The extent of exposure in pregnancy during clinical trials should be included:

Wide: >1,000 pregnancies²;
Limited: <1,000 pregnancies;
Very Limited: individual cases only;
No experience.

It should be indicated when the drug is not absorbed systemically and not known to have potential for indirect harm to the fetus.

Breast-feeding: Where a drug is absorbed systemically, information about the excretion of the drug in human milk and effects on the nursing infant should be included. Adverse reactions expected in the infant should be provided and suggested measures to avoid high level exposure to the infant should be presented. The potential for serious adverse reactions or tumourgenicity should be clearly stated.

In the absence of human data, pertinent animal data should be included (e.g., adverse reactions, concentration detected in the milk plasma ratio) and the following or similar statement should be used:

It is unknown if the drug is excreted in human milk. Because many drugs are excreted in human milk precaution should be exercised.

Pediatrics: This subsection should contain specific monitoring and hazards associated with pediatric use of the drug. The term pediatric generally pertains to persons between birth and 18 years of age, but it is recognized that this may not apply to all products, therefore the Pediatric subtitle should include the age upon which the pediatric recommendation is based. For example, 12 years of age should be used if the clinical trials included only children up to the age of 12. If pediatric patients were included on the basis of criteria other than age (e.g., by weight, without a specified age range), this should be reflected here instead.

² Extent of exposure categories are based on Council for International Organizations of Medical Sciences (CIOMS).

In the absence of a Health Canada authorized pediatric indication, this subsection should repeat that the product is not indicated in the pediatric population. One of the following or similar statements should be used:

Pediatrics (age range): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

or

Pediatrics (age range): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of [Brand name] in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use. [Include cross-reference to relevant sections.]

Information about specific known safety risks associated with use of the product in the pediatric population should be reflected here (regardless of indication status), indicating the age range impacted, where known. Warnings should focus on events which are different from, or more severe than those seen in adults. An accompanying statement should explain that warnings applicable to adults are also relevant to pediatric use. Presentation of short-term versus long term exposure warnings may be relevant, if there are differences.

Geriatrics: This subsection should contain specific monitoring and hazards associated with geriatric use of the drug. Cross-reference to renal and hepatic subheadings where appropriate. The term geriatric generally pertains to persons over 65 years of age but it is recognized that this may not apply to all products, therefore the Geriatric subtitle should include the age upon which the geriatric recommendation is based. For example, 75 years of age would be used if the study data included only the frail elderly.

3.8 Adverse Reactions

3.8.1 Definitions and Terminology

The application of the Adverse Reaction section of the guidance depends in part on the interpretation of the following terms: “adverse reaction”, “adverse event”, and “serious adverse reaction”.

“Adverse reaction”, for the purpose of this guidance, is an unintended event, reasonably associated with the use of a drug and conforms to the regulatory definition of “adverse drug reaction³”.

³ C.01.001, *Food and Drug Regulations*

An “adverse event”, for the purpose of this guidance, does not necessarily have a causal relationship to the drug. If there is any reason to suspect the event is related to the use of a drug, the event is likely an adverse reaction.

A “serious adverse reaction”, for the purpose of this guidance conforms to the regulatory definition of “serious adverse drug reaction⁴”.

See the Glossary section for more detailed definitions.

Medical Dictionary for Regulatory Activities (MedDRA)

MedDRA (www.meddra.org) should be used as the preferred terminology to describe adverse reactions. This will be at the Preferred Term (PT) Level, although there may be instances where the use of a Lowest Level Term (LLT) or a High Level Term (HLT) may be appropriate. Indicate the version of MedDRA used for the data described.

Adverse reactions that are reported under different terms in the database, but that represent the same phenomenon (e.g., sedation, somnolence, drowsiness) or disease pathophysiology in more than one body system (e.g., congestive heart failure: nocturnal dyspnoea, angina, pedal oedema) should be grouped together as a single adverse reaction to avoid diluting or obscuring the true effect.

Council for International Organizations of Medical Science (CIOMS)

The standard for defining frequency terms will be based on the CIOMS convention as indicated below:

Very common: $\geq 1/10$ ($\geq 10\%$);

Common (frequent): $\geq 1/100$ and $< 1/10$ ($\geq 1\%$ and $< 10\%$);

Uncommon (infrequent): $\geq 1/1,000$ and $< 1/100$ ($\geq 0.1\%$ and $< 1\%$);

Rare: $\geq 1/10,000$ and $< 1/1,000$ ($\geq 0.01\%$ and $< 0.1\%$);

Very rare: $< 1/10,000$ ($< 0.01\%$), including isolated reports.

3.8.2 General Information

The Adverse Reaction section contains information on adverse reactions identified during clinical trials and as a result of post-market surveillance. Information relating to clinical trial adverse reactions and post-market adverse reactions should be presented separately, in a clear and logical manner and be included in a table where possible. The information to be included will be determined in consultation with Health Canada.

⁴ C.01.001, *Food and Drug Regulations*

The following factors may be considered for the inclusion of adverse reactions:

- frequency of reporting;
- frequency exceeds that of placebo or control;
- evidence of dose-response;
- time relationship and evidence of de-challenge or re-challenge;
- consistency with pharmacology of the drug;
- class effect;
- serious events including those rarely seen and that occur generally in association with drug therapy. These adverse reactions should be listed even if there are only one or two reported events, unless it is clear that a causal relationship can be excluded. Examples include:
 - liver failure;
 - agranulocytosis;
 - rhabdomyolysis;
 - idiopathic thrombocytopenic purpura;
 - intussusception
 - hypersensitivity.

Inclusion of events which are infrequent and minor, commonly observed in the absence of drug therapy or not plausibly related to the drug should be avoided. Note that at this time there are no universally accepted algorithms to assess causality in support of converting adverse events to adverse reactions. Results of significance testing should be omitted unless they provide useful information and are based on a pre-specified hypothesis in an adequately designed and powered study.

3.8.3 Adverse Reaction Overview

The purpose of this subsection is to summarise the adverse reaction information that would be most useful to the prescriber, e.g., that may affect prescribing decisions or would be useful in observing, monitoring or advising patients. Serious and/or unexpected adverse reactions described in other sections of the product monograph should be cross-referenced here. Avoid subjective terms (e.g., *well-tolerated*) since they are non-specific, promotional and/or poorly defined.

This subsection should highlight the following:

1. Serious adverse reactions;
2. The most frequent adverse reactions (e.g., those occurring at a rate of 10% or greater);

3. Adverse reactions that most commonly result in clinical intervention such as:
 - discontinuation;
 - dose modification;
 - concomitant medication to treat an adverse reaction symptom;
 - close monitoring;
4. Factors that may affect the rate or severity of a reaction:
 - disease state;
 - concomitant therapy;
 - demographic subgroup;
 - dose;
 - duration of therapy (e.g., adverse reactions that appear in the beginning of treatment but usually resolve with continuous treatment, or adverse reactions that may only appear with longer term treatment);
5. In some cases it may be appropriate to list the serious adverse reactions that are typical for the drug class, but have not been specifically observed in the clinical trials with this particular drug.

Presentation: narrative

3.8.4 Clinical Trial Adverse Reactions

General Statement

To provide a common understanding when interpreting adverse reaction data from all clinical trials, the following or similar statement should precede this subsection:

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Description of data sources

The presentation of adverse reaction data should be preceded by a clear, brief, description of the data source. Information should include overall exposure (e.g., number of patients, dose, schedule, duration of treatment), patient population, demographics, and a brief description of the study design (e.g., placebo-controlled, active-controlled), composition of control group, any critical exclusions, and any other relevant information.

Relative Frequency of Adverse Reactions

The frequency of a particular adverse reaction should be derived from all treatment-emergent adverse events, independent of the investigator's opinion on the relationship to the study drug.

Whether comparator data would be included or not in this subsection of the product monograph, should be based on consultation with Health Canada.

Common and very common adverse reactions (those with frequency rates $\geq 1\%$) should be presented in a table. The frequency cut-off for the listing of common adverse reactions identified from clinical trials should be appropriate to the size and composition of the safety database and should be determined in consultation with Health Canada. The frequency cut-off should be noted in the table header and the text accompanying the table.

A single table is preferable. Multiple tables are appropriate when the drug's adverse reaction profile differs substantially from one setting to another. The content of the additional tables should be limited to only those adverse reactions for which there were meaningful differences in rates. Important differences may result from:

- different product indications;
- formulations;
- population subgroups;
- study durations;
- dosing regimens;
- types of studies (e.g., intensely monitored versus a large outcome study).

Data in the primary adverse reactions table should be derived from clinical trials submitted in support of the proposed indication.

The table should indicate:

- patient population from which the data was derived;
- dose and dose regimens used (fixed or flexible, up-titration, etc.);
- duration of the treatment period;
- basis for inclusion in the table (e.g., all adverse reactions at incidences above a threshold and higher than in the placebo or control group);
- data source used to derive the frequencies (e.g., treatment-emergent adverse events);
- number and percentage of patients in each treatment group.

Frequencies should generally be rounded off to the nearest integer. An exception would be for particularly serious adverse reactions occurring at low frequencies in a large study where fractions of a percent may be meaningful;

Information should be categorized by system organ class (SOC) proposed by MedDRA according to the following hierarchal structure:

- 1st - by SOC in alphabetical order;
- 2nd - then by decreasing frequency within each SOC.

Where relevant, adverse reactions due to drug discontinuation should be presented separately and the method used to collect the data should be indicated (e.g., voluntary reporting or applied questionnaire).

The data table should be followed by a brief narrative to supplement the information in the table and include where applicable, the following:

- ***Dose-response information:*** identify adverse reactions that exhibit a dose-response and describe the manner in which dose-response was investigated.
- ***Special Populations:*** information about observed differences in adverse reaction rates in various demographic groups or disease subsets.
- Information on dosage and duration of therapy linked to adverse reactions.

Presentation: table and narrative (see template). Graphs should not be used to present adverse reaction information.

3.8.5 Less Common Clinical Trial Adverse Reactions

This subsection should present clinical trial adverse reactions with a frequency below the specific cut-off for inclusion in the table of common and very common adverse reactions. The less common adverse reactions should be presented as a listing and categorized by SOC, alphabetically.

Generally, one list of less common reactions is presented, with pooled data including controlled and uncontrolled trials relevant for the characterisation of safety for the authorized indications, unless there are major differences between studies or populations.

Presentation: list

3.8.6 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and other Quantitative Data

Clinically significant changes in laboratory findings identified during clinical trials should be summarized in table format. Where applicable, there should be one table for hematologic changes, one for chemistry changes, and one for quantitative data (e.g., electrocardiograms). The laboratory parameters should be listed in alphabetical order. The table should define the magnitude of change from normal values that was considered clinically significant, and the number of patients and percentage of the population that met the criteria.

Presentation: table

3.8.7 Clinical Trial Adverse Reactions (Pediatrics)

Adverse reactions observed in trials supportive of the indication for use in the pediatric population should focus on reactions which are more frequent, more severe, or different from those seen in adults. An accompanying statement should explain that reactions applicable to adults are also relevant. Presentation of short-term versus long term exposure warnings may be relevant, if there are differences. In this context, extensive tables of adverse reactions should not be presented. A text description of clinically important reactions is preferred.

In the absence of a Health Canada authorized pediatric indication, and only where there are important safety differences between adults and children, brief information should be presented on observed clinical trial adverse reactions.

Presentation: narrative

3.8.8 Post-Market Adverse Reactions

This subsection should include Canadian and international post-market adverse reactions including serious and/or unexpected adverse reactions that are reported through post-market surveillance and/or identified in Phase IV clinical trials. For guidance relating to the determination of serious adverse reactions and further information, please refer to the Health Canada *Guidance Document for Industry - Reporting Adverse Reactions to Marketed Health Products*.

The following factors may be considered for the inclusion of post market adverse reactions:

- seriousness of event;
- number of reports;
- strength of causal relationship;
- new events;
- increase in severity and/or frequency over adverse reactions observed in clinical trials;
- class effect.

Adverse reactions already listed in the Clinical Trial Adverse Reactions section should not be repeated in this section unless there are changes in severity, frequency or character.

This subsection of the product monograph, as well as other related sections affected by new safety information should be updated according to the most recent available safety data from Phase IV clinical trials or spontaneous reports for the drug, or according to product monograph updates in the drug class.

Presentation: Narrative. If the volume warrants, the information should be presented in a table using the same format as Clinical Trial Adverse Reactions.

3.9 Drug Interactions

This section should contain practical guidance for the prevention or management of drug interactions. The mechanism of the interaction should be briefly stated.

3.9.1 Serious Drug Interactions Box

Serious (e.g., life-threatening) interactions should be included here in a brief statement, with a cross-reference to detailed information in the drug interaction subsections (e.g., Drug-Drug Interactions). If a drug interaction is included in the Contraindications or Serious Warnings and Precautions Box it must also be included in this box. Text should generally not exceed 20 lines. If there are no serious drug interactions, this box may be omitted.

Presentation: bullet form within a box (see template)

3.9.2 Overview

Potential interactions should be presented in the Overview subsection. This would include interactions suspected based on the pharmacokinetic or pharmacological profile of the drug (e.g., cytochrome P450 interactions, QT interval prolongation potential, genetic polymorphism). This information should be presented in narrative format. A brief statement about the potential mechanism of the potential interaction should be presented.

Drug class statements should appear here if the interaction has not yet been documented but would be clinically significant. When a potential drug class interaction is considered clinically significant, representative drugs from that class should be added to the drug interactions table.

The information in this subsection is based on clinical relevance and will be determined in consultation with Health Canada.

The potential interaction with alcohol should be discussed briefly.

Presentation: narrative

3.9.3 Drug-Drug Interactions

All clinically relevant drug-drug interactions (including those only supported by animal or *in vitro* studies) should be presented in this subsection.

Pharmacokinetic studies presenting information regarding the kinetics of specific drug combinations should be presented here. The following or similar statement should be included before the table:

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Where no interaction data is known the following or similar statement should be included:

Interactions with other drugs have not been established.

Presentation: table format. Where data is limited, the information may be better presented in narrative format. The table should list the proper (or common) name of the drugs, the source of evidence for the interaction (e.g., case study, clinical trial or

theoretical), the effect and a clinical comment. See the template for an example of a drug-drug interaction table.

3.9.4 Drug-Food Interactions

This subsection should briefly present known or potential interactions with food or beverages (e.g., grapefruit juice, caffeine) and practical guidance for the health professional. The composition of a meal should be described when this may affect the pharmacokinetics (e.g., high fat content meals) of the drug product. Cross-referencing to the Dosage and Administration section may be required when the timing of food consumption with respect to drug administration could avoid or worsen the interaction. Interactions caused by different formulations of the drug should be indicated.

Where no interaction data is known, the following or similar statement should be included:

Interactions with food have not been established.

Presentation: brief narrative.

3.9.5 Drug-Herb Interactions

This subsection should briefly present known or potential interactions with herbal products and practical guidance for the health professional.

Where no interaction data is known, the following or similar statement should be included:

Interactions with herbal products have not been established.

Presentation: brief narrative.

3.9.6 Drug-Laboratory Test Interactions

This subsection should briefly present laboratory tests affected by the presence of the drug, such as interfering with the accuracy of the test results or methods (e.g., antihistamines diminish the positive reactions to dermal reactivity indicators). Practical guidance for the health professional should be included.

Where no interaction data is known, the following or similar statement should be included:

Interactions with laboratory tests have not been established.

Presentation: brief narrative.

3.9.7 Drug-Lifestyle Interactions

This subsection should briefly present interactions with lifestyle choices (e.g., smoking) and practical guidance for the health professional.

Where no interaction data is known, this subsection can be omitted.

Presentation: brief narrative.

3.10 Action and Clinical Pharmacology

This section should include a concise synopsis of the salient features of the drug's mechanisms of action, pharmacodynamics and pharmacokinetics. The information should have a demonstrated relevance to the safe and effective use of the drug in humans. Relevant animal data (e.g., safety pharmacology) should be included only where human studies are lacking or deficient, or where the information is relevant to interpretation of toxicity or mode of action.

3.10.1 Mechanism of Action

This subsection should briefly describe the established mechanism through which the drug produces its pharmacologic effects for both the therapeutic action and the drug toxicity. The mechanism of action should be described at the cellular or receptor/enzyme level and in relation to the target organs and the whole body, depending on what is known. If the mechanism of action in relation to the therapeutic effects is unknown, this should be stated.

A brief description of the disease pathophysiology may be included if it improves the understanding of the drug's pharmacology.

For anti-infective drugs, a brief description of the action of the drug against microorganisms or enzyme systems involved in replication should be included.

Presentation: brief narrative

3.10.2 Pharmacodynamics

This subsection should briefly describe the reasonably well-established therapeutic as well as unintended (toxic) effects of the drug, including active metabolites, where applicable.

The following information should be included:

- The principal pharmacodynamic effects related to the therapeutic action. Effects on mechanistically important biomarkers should be included.
- Receptor/enzyme selectivity if there is data to indicate this may be related to therapeutic action or toxicity.
- Dose response and related pharmacokinetic/pharmacodynamic (exposure/response) analyses, including the time to onset, magnitude and duration of the pharmacodynamics effects in relation to exposure.
- Pharmacologic effects relevant to safety.
- Tolerance, rebound effects, potential for abuse, dependence and withdrawal effects.
- Factors affecting pharmacodynamic effects (e.g., interactions via cytochrome P450, drug transporters, genetic polymorphism, antibody formation). This should not include drug interaction information which is presented under section 3.9 Drug Interactions.
- A factual description of any effects of the drug on ECG intervals (e.g., QTc, QRS, PR) and ventricular heart rate should be provided, including dose and duration of treatment and magnitude of effect. Lack of any effect on these parameters should also be stated in the context of the exposures studied. In exceptional situations in which optimal ECG data might be lacking, a statement should be included noting this deficiency or describing the best available alternative data. These data should be presented under a separate subheading (e.g., Cardiac Electrophysiology, Electrocardiography).

Presentation: brief narrative

3.10.3 Pharmacokinetics

This subsection should include a brief statement describing whether the drug exhibits linear or non-linear pharmacokinetics. If non-linear, the nature of non-linearity, including the dose range over which the non-linearity is observed as well as the underlying mechanism of non-linearity, should be described.

A summary of the most clinically relevant pharmacokinetic parameters for the drug, including active metabolites should be presented in a table (see template). The table should include: maximum observed concentration (C_{max}), area under the curve (AUC),

time to maximum observed concentration (t_{\max}), volume of distribution (Vd), elimination half-life ($t_{1/2}$) and clearance (CL).

Generally, the pharmacokinetic data from a healthy population should be presented. If meaningfully different from the healthy population, the pharmacokinetic data from patient population(s) for which the drug is indicated should also be included.

The summary table should be followed by a brief explanation of the following, under appropriate subheadings.

Absorption: Bioavailability, whether absorption kinetics are linear or nonlinear over the range of doses and concentrations, food effect on absorption (even if negligible) and time to steady state;

Distribution: Degree of protein binding, sites of distribution, rate and extent of uptake by target organs if clinically relevant, and whether the drug crosses the blood-brain barrier. Placental transfer and secretion into milk should be described under the Special Populations and Conditions subsection;

Metabolism: Sites and pathways of metabolism (e.g., p-glycoprotein, cytochrome P450) and extent of first-pass metabolism, metabolites and their activity, dose dependent changes in metabolism, effect of the drug, including active metabolites, on metabolic pathways (e.g. inhibition or induction of p-glycoprotein, cytochrome P450). If these effects result in clinically relevant drug interactions, a cross-reference to the Drug Interactions section should be included;

Elimination: Route(s) of excretion and the percentage of the drug, including active metabolites, excreted by each route, and the mechanisms of the excretory routes. If the drug is not excreted but eliminated by metabolism (e.g., large proteins), or if it is eliminated by both excretion and metabolism, this should be stated.

This subsection should include pharmacokinetic information that is relevant to special populations [e.g., pediatrics, geriatrics, sex, pregnancy and breast-feeding (placental transfer and secretion into milk), genetic polymorphism, ethnic origin] and certain conditions (e.g., hepatic insufficiency, renal insufficiency, obesity).

Where a pediatric indication has not been granted by Health Canada, it may still be useful to include the results of pharmacokinetic studies in children that have been submitted to Health Canada, if these results provide useful information for the prescriber. However, the fact that a pediatric indication has not been granted by Health Canada should be restated here, with a cross-reference to applicable sections (e.g., Warnings and Precautions, Adverse Reactions).

Presentation: table (for pharmacokinetic values) and narrative (see template)

3.11 Storage, Stability and Disposal

This section should specify the recommended storage conditions for each dosage form. If dispensing in a particular type of container (such as a light-resistant container) is necessary, this should be stated. If a change in a physical attribute is known to occur (including colour or clarity) during storage, an appropriate warning and significance of the change should be included.

All labelled storage recommendations should be supported by appropriate stability studies.

For reconstituted products, including parenterals, the recommended storage period and conditions for each solution should be stated. In view of the potential risks from microbial contamination during preparation of parenterals that do not contain a preservative, recommended storage periods should not exceed 24 hours at room temperature (15 to 30°C) and 72 hours under refrigeration (2 to 8°C) and can be much shorter, depending on the product.

Any known incompatibilities should be stated, including incompatibilities between drugs, diluents or infusion fluids, primary packaging, or administration sets, or with any other material with which the drug may come into contact.

Disposal instructions should be included for all drug products. For those potentially hazardous drug products, include a cross-reference to more detailed safe disposal instructions under the Special Handling Instructions section.

The following or similar statements should be included when appropriate:

Temperature:

Store under refrigeration (2 to 8°C).

Store at room temperature (15 to 30°C).

Light:

Protect from exposure to light.

Moisture:

Protect from moisture.

Protect from high humidity.

Others:

Keep out of reach and sight of children.

Presentation: narrative

3.12 Special Handling Instructions

Any special handling instructions for people who are likely to come into contact with potentially hazardous products during preparation or during administration to patients should be clearly specified. This is of special importance for hazardous drugs that may be mutagenic (e.g., cytotoxic drugs). When necessary, special instructions should be included for the decontamination and safe disposal of drugs and associated material.

Presentation: narrative

4 PART II: SCIENTIFIC INFORMATION

4.1 Pharmaceutical Information

4.1.1 Drug Substance

This subsection should include information on the drug substance under the following headings:

- a) Proper name or common name;
- b) Chemical name;
- c) Molecular formula and molecular mass;
- d) Structural formula, including relative and absolute stereochemistry;
- e) Relevant physicochemical properties, for e.g., physical description, solubilities over the physiological pH range (pH 1-8), polymorphic form.

4.2 Clinical Trials

The clinical trials section of the product monograph should contain data from the main studies in support of the drug's efficacy and safety and should generally not include other information as this section is not intended to be a comprehensive reference of all studies related to the drug product.

The detailed information should address the following major components:

- study design,
- study population,
- disposition of subjects, and
- results of study endpoints that support the efficacy and safety of the drug, including estimated treatment effects and the corresponding measures of uncertainty (ρ -values and confidence intervals).

The information on clinical trials should be presented in a tabular format for ease of retrieval of the information. The demographic and baseline characteristics data should be presented in one table (see template) with the aggregate results provided in a separate table.

This section should also include comparative bioavailability studies, as required, for revised formulation and new dosage forms.

4.2.1 Efficacy and Safety Studies

Trial design and Study Demographics

This subsection should describe the major design characteristics of the study, including:

- type of control,
- level of blinding (e.g., double-blinded),
- how subjects were assigned to treatment groups (e.g., randomized),
- route of administration,
- treatment arms (doses administered), and
- duration of therapy.

The description of the study population should include a summary of key inclusion and exclusion criteria as well as summary statistics on baseline demographic and disease characteristics.

Endpoints used to establish the efficacy of the drug should be described. In the table displaying the study results, details regarding the statistical methods used to analyse these endpoints, including the procedures for multiplicity control, should be captured as a footnote.

Studies that should be included should be carefully planned, properly designed and well conducted studies that support the efficacy, safety and dosing regimens for the drug and studies that provide information about the limitations of effectiveness.

Studies that should not be included are studies that:

- imply or suggest effectiveness for an unauthorized indication;
- present the incidence, frequency, or severity of adverse reactions and are not the subject of an acceptable NDS, SNDS or Notifiable Change (NC) submission.

The following points should be taken into consideration when an active comparator is utilised in a given clinical trial:

- The active comparator should be used as indicated in its Canadian product monograph (e.g., same target population, dosage, route of administration and single or multiple drug therapy).
- For non-inferiority and equivalence trials, the selection of the comparability margin should be clearly justified.
- The comparator should be reported by its proper or common name.

Presentation: Table and narrative (see template)

Study Results

Results of study endpoints that support the efficacy and safety of the drug, including estimated treatment effects and the corresponding measures of uncertainty such as p -values and confidence intervals while accounting for multiple testing, should be presented.

Clinically relevant results from subgroup analyses that are considered to be of particular interest could be acceptable following consultation with Health Canada, with the caveat that the results should be interpreted with caution given the inherent risks with subgroup analyses in general.

More than one table may be required to capture results (e.g., different indications, different age groups, etc.).

Presentation: table (see template)

4.2.2 Pivotal Comparative Bioavailability Studies

- For all revised formulations and new dosage forms whose safety and efficacy is supported solely on the basis of comparative bioavailability studies, a summary of the study should be provided in table format.
- This table should be preceded by a narrative outlining the design of the comparative bioavailability study (i.e., single/multiple dose, fasting/fed, crossover/parallel, dose/number of dosing units, number of healthy male/female

volunteers/patients). The narrative should incorporate the identities of the compared products.

Presentation: table and narrative (see template)

4.3 Microbiology

This section is needed for all antimicrobial drugs. It is to comprise laboratory studies and be divided, where appropriate, into *in vitro* and *in vivo* subsections. It should also contain a description of the microbiological data that supports the pathogen(s) for the authorized indication, and that supports the microbiological information summarized under section 3.10 Action and Clinical Pharmacology.

Details regarding interpretive criteria, standards for susceptibility testing, and standards for reference pathogens, should be included (as per current acceptable standards). Information on drug resistance and cross-resistance should be included.

Presentation: table(s) and narrative

4.4 Non-clinical Toxicology

This section should include a brief description of the non-clinical toxicology findings which are relevant for the safe use of the drug and/or contribute to the understanding of a drug's toxicological profile. It is expected that only the most relevant findings will be described in this section. For each study described, and where applicable, the species, route of administration, dosage regimen (e.g., dose levels, frequency of administration, duration of dosing, formulation), relevant findings, the No Observed (Adverse) Effect Level and/or Lowest Observed (Adverse) Effect Level, and calculated margins of exposure should be provided.

The data should be presented in the following order under appropriate subheadings:

- General Toxicology (single and repeat-dose studies). The studies described under this subheading should be limited to those studies needed to support market authorization (e.g., 6 month study in rodents, 9 month study in non-rodents⁵).
- Carcinogenicity. Study results that demonstrate a drug's carcinogenic potential should be described. If a drug does not exhibit carcinogenic potential, or the carcinogenic potential has not been fully evaluated, this should be stated. Tumour findings considered relevant to the safe use of the drug should be briefly described in the Warnings and Precautions section, with a cross-reference to the information provided here.

⁵ ICH Guidance On Nonclinical Safety Studies For The Conduct Of Human Clinical Trials And Marketing Authorization For Pharmaceuticals, M3(R2), June 11, 2009

- **Genotoxicity.** Study results that demonstrate a drug's genotoxic potential should be described. If no genotoxic effects are identified, or the genotoxic potential has not been fully evaluated, this should be stated, with a summary of the types of studies conducted. Findings considered relevant to the safe use of the drug should be briefly described in the Warnings and Precautions section, with a cross-reference to the information provided here.
- **Reproductive and Developmental Toxicology.** Only findings that are toxicologically meaningful should be described. In cases where a drug does not demonstrate reproductive and/or developmental toxicities, or the reproductive potential has not been fully evaluated, this should be stated. Findings considered relevant to the safe use of the drug should be briefly described in the Warnings and Precautions section, with a cross-reference to the information provided here.
- **Special Toxicology Studies.** Studies briefly described under this subheading may include photosafety, immunotoxicity, abuse liability, combination drug toxicity, etc. Important mechanistic studies may also be included unless it is more relevant to present them under other subheadings (e.g., General Toxicology, Carcinogenicity).
- **Juvenile Toxicity:** Where the drug is indicated or likely to be used in the pediatric population, the results from studies in juvenile animals should be presented, when available.

Presentation: Narrative where possible. Table format only where presentation is made more concise. Information should only be presented once, either in narrative or table format.

4.5 Supporting Product Monographs

This section should list only those Health Canada authorized product monographs that were supportive in the development of the product monograph (e.g., for certain generic drug products, subsequent market entry drug products, or combination products). As an example, a generic drug product would only list the product monograph for the Canadian Reference Product to which it was compared. The following or similar format may be used:

<Brand name> <(dosage form, strength)>, submission control <number>, Product Monograph, <sponsor>. <(MON, DD, YYYY)>

Where there are no supporting product monographs, this section should be removed from the product monograph.

References should not be included unless requested by Health Canada under special circumstances. These should be included within the relevant section of the product monograph (e.g., within the text or as a footnote on the page where it was cited) and follow the Uniform

Requirements for Manuscripts from the International Committee of Medical Journal Editors (<http://www.icmje.org/about-icmje/faqs/icmje-recommendations/>), found in *Citing Medicine*⁶

Presentation: numbered list

5 PART III: PATIENT MEDICATION INFORMATION

5.1 Introduction

The Patient Medication Information section is a plain language translation of information contained in Parts I and II of the product monograph. Plain language means using the simplest, most common words possible, so that information is clear, concise and easy to understand for the intended audience.

For the purposes of the product monograph, "patient" is defined as the general public. This may include an individual using the drug, a caregiver or someone who is simply interested in obtaining information about a drug.

Part III should be produced as part of the product monograph for all drugs that are required to comply with this guidance document. This applies to all drugs regardless of administration setting (e.g., hospital use only, emergency), because the ultimate audience is the general public.

The content for this section will be determined in consultation with the sponsor and Health Canada and is limited to information found in Parts I and II.

If there are other drug-specific guidelines [e.g., “*Basic Product Monograph Information for Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)*”, *Bureau of Metabolism, Oncology and Reproductive Sciences, November 2006*], this information should also be incorporated into Part III.

Where information is substantially different for each indication (e.g., diagnosis versus treatment/therapy), route of administration or formulation of the product, a separate Patient Medication Information section is warranted for each. For example, a product that is indicated for migraine and hypertension would have two Patient Medication Information sections.

5.2 Language

Recognizing that there are different audiences for this information, for consistency, the Patient Medication Information section should be written as if it will be read by an individual who will

⁶ Patrias K. *Citing medicine: the NLM style guide for authors, editors, and publishers* [Internet]. 2nd ed. Wendling DL (technical editor). Bethesda: National Library of Medicine (US); 2007 (updated 2011 Sep 15). <http://www.nlm.nih.gov/citingmedicine>

use or be administered the drug. For drugs where the patient is not an active participant (e.g., inhaled anaesthetics or other drugs, such as radiopharmaceuticals, that are administered under special conditions), the language may be adjusted.

Health literacy levels in Canada vary significantly among regions and demographically. For this reason, language should be adjusted for lower literacy levels. Assume that the reader has no prior knowledge of the medication or how to use it. Use the simplest, shortest words possible.

It is the responsibility of the sponsor to ensure that any translations of the Patient Medication Information section accurately reflect the meaning of the original authorized version.

In developing the Patient Medication Information section, sponsors are strongly encouraged to get help from appropriate plain language resources, including the Canadian Public Health Association and their publication *Good Medicine for Seniors: Guidelines for Plain Language and Good Design in Prescription Medication*⁷. The guidelines in this document show how to write health information in plain language for patients (for both prescription and non-prescription drugs), and include a compendium of plain language terminology. Sponsors would also benefit from user-testing their patient medication information for comprehension.

5.3 Style Guide

These style guide recommendations apply to the Product Monograph Part III as well as any patient medication information documents or leaflets that are produced as part of the drug product packaging.

- The Patient Medication Information section should not be promotional in tone or content. The text should be factual and avoid vague generalizations.
- Brand name should be used in the headings and the text.
- Page layout: left-justified.
- Margins:
 - (a) Product Monograph Part III - 2.5 centimetre (1") top, bottom and sides
 - (b) Patient Medication Information leaflet - 0.75 cm (0.3") top, bottom and sides
- Font:
 - (a) Product Monograph Part III - Sans Serif type fonts (e.g., Calibri 12 point, Arial 11 point);

⁷

Canadian Public Health Association, 2002

(b) Patient Medication Information leaflet - Sans Serif type fonts (such as Arial or Calibri) are recommended, text - 10 point and tables - 9 point. Flexibility will be exercised in those situations where a smaller font may be necessary due to packaging constraints or printing limitations. Legibility is the goal and sponsors are responsible for ensuring that the Patient Medication Information, as it appears on the leaflet, is clear and easy to read to the patient under the customary conditions of purchase and use.

A person with normal vision, or those with corrective glasses that restore normal vision, should be able to read the information without straining. The colour, contrast, the position, and the spacing of the information are all to be taken into consideration in complying with these requirements.

- Headings and Subheadings: bold type face should be used. Italics and underlining should be avoided. All upper case font should also be avoided except where instructed (e.g., READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE, PATIENT MEDICATION INFORMATION and BRAND NAME at the beginning of the Patient Medication Information section).
- The information should be as brief and succinct as the requirements of the guidelines allow.

5.3.1 Illustrations

Illustrations that help demonstrate the proper use of a self-administered product (e.g., inhaler, injectable product) are encouraged.

Pictures or graphics can often be misleading as to the use, merit, and character of a drug product and should be avoided. Pictograms should not be used.

5.4 Readability and Usability

To ensure the Patient Medication Information section can be understood:

- Aim for a Grade 6 - 8 reading level. Tests and resources are available in libraries and on-line to ensure the readability of text such as the Flesch-Kincaid, Fry Graph Readability Formula and SMOG (Simple Measure of Gobbledygook) health literacy readability tools.
- The Patient Medication Information section should be simple, clear and easy to understand so that patients are able to find, understand and act upon the information. Consider these tips:
 - Write directly to your reader, using the first person (you, we).

- Use clear, positive instructions (e.g., **Instead of:** Do not take this medicine on an empty stomach. **Say:** Take this medicine with food.).
- Write instructions consecutively (i.e., in the order you want them carried out).
- Use the shortest, most common words possible (e.g., **Instead of:** You may experience edema of the legs. **Say:** Your legs may swell.).
- Avoid acronyms, abbreviations, foreign terms and technical jargon. If you must use a technical term, define it in plain language immediately after the word.
- Use active (rather than passive) voice. Make sure the subject is named and acts on the object, and keep the subject close to the verb (e.g., **Instead of:** This medication is to be taken before every meal by your child. **Say:** Give your child this medication before every meal.).
- Where possible, use bulleted information instead of sentences and paragraphs. When sentences are necessary, keep them short with one idea in each sentence. Break up long text and remove unneeded words.
- Use minimal punctuation. If there are a lot of commas and semicolons, the sentences are likely too long.
- For long lists, use a bulleted list (instead of paragraph format).
- When using numbers, numerals are easier to read than written words (e.g., 53, instead of fifty-three). Where appropriate, include imperial equivalents in brackets after metric measurements, since many seniors and people from other countries use imperial.

5.5 Using the Template

5.5.1 General

A template of the Patient Medication Information section has been provided in Appendix E - I (as part of the product monograph templates).

There should be a header placed on the first page of the monograph with the words in upper case "READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE".

At the beginning of the document, the brand name of the drug should appear in upper case, with the proper name of the drug in final dosage form in lower case appearing below the brand name. Where there is no proper name, use the common name in final dosage form. Consider adding, in brackets, a phonetic spelling of the brand name or proper name. If a phonetic spelling of the brand name is included, it should be on the line preceding the brand name. If a phonetic spelling of the proper name is included, it should be on the line following the proper/common name.

When there is a boxed statement in any section of Part I or II, a corresponding boxed statement, in plain language, should appear in the relevant section of Part III.

5.5.2 Opening Disclaimer

The following or similar statement should be included for all drugs:

Read this carefully before you start taking <Brand name> and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about <Brand name>.

5.5.3 About the Medication

Heading: “What is <Brand name> used for?”

Provide a bullet listing of the indications from Part I. If the Indications section includes lifestyle recommendations as part of the therapy (e.g., diet as adjunctive therapy for antidiabetic drugs) they should be included here.

Heading: “How does <Brand name> work?”

From the Action and Clinical Pharmacology section of Part I, provide one or two sentences, explaining the mechanism of action of the drug, in plain language. From the Action and Clinical Pharmacology section of Part I and Clinical Trials section of Part II, indicate how long it takes to work and how to know if it is working (e.g., improved symptomatology).

Heading: “What are the ingredients in <Brand name>?”

This section should include a complete listing of all medicinal and all non-medicinal ingredients, from Part I. Medicinal ingredients should be clearly separated from the non-medicinal ingredients with the headings “Medicinal ingredients” and “Non-medicinal ingredients”.

List medicinal ingredients by their proper names; where there are no proper names, use common names.

List non-medicinal ingredients in alphabetical order, using either proper, common or international nomenclature.

Heading: “<Brand name> comes in the following dosage forms:”

From the Dosage Forms, Strengths, Composition and Packaging section of Part I, provide the available marketed dosage forms and strengths. List the name of the dosage form followed by the strengths in increasing order (e.g., tablet 10 milligrams, 20 milligrams, 100 milligrams).

Heading: “Do not use <Brand name> if:”

For each situation described in the Contraindications section of Part I, include a corresponding situation in a bulleted list, in plain language, where appropriate.

5.5.4 Warnings and Precautions

This section should include serious issues/precautions associated with the use of the drug. Using as few words as possible, and where appropriate, explain the importance of a warning or precaution (i.e. why).

Serious Warnings and Precautions Box

When there is a Serious Warnings and Precautions box, it should be placed after the opening disclaimer. Only when there is a Serious Warnings and Precautions box in Part I, should a corresponding box appear in Part III.

The boxed information should contain the heading “**Serious Warnings and Precautions**” and briefly detail, in bulleted form, serious concerns associated with using this drug. The box should contain a plain language version of the same information that is provided in the Serious Warnings and Precautions Box in Part I. Adjustment of this information, if necessary, will be determined in consultation with the sponsor and Health Canada. Cross-references to other sections of Part III may be included.

Heading: “To help avoid side effects and ensure proper use, talk to your healthcare professional before you take <Brand name>. Talk about any health conditions or problems you may have, including if you:”

Enter one point for each warning and precaution from Part I in a bulleted list, in plain language.

Heading: “Other warnings you should know about:”

This section is included only when there are other general warnings and precautions that are not serious and do not fit under existing headings.

The following or similar statement may be used if there are effects described in Part I that may impair performance of a task requiring special attention, including driving and operating machinery:

Give yourself time after taking <Brand name> to see how you feel before driving a vehicle or using machinery.

5.5.5 Interactions

Heading: “Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.”

Heading: “The following may interact with <Brand name>:”

Provide a bulleted list.

This section is to ensure patients are aware of any medications, foods (e.g., citrus, dairy), beverages (e.g., alcohol) or natural health products known to interact with this medication. Serious or significant interactions should be listed in bullet form (for example drug interactions listed in the Serious Drug Interactions box in Part I). If no relevant interactions are known, add a statement to reflect this.

5.5.6 Proper Use

Heading: “How to take <Brand name>”:

This section is intended to provide information on how to prepare, reconstitute or administer the drug or operate a device (e.g., metered dose inhaler).

Illustrations that help demonstrate the proper use of a self-administered product (e.g., inhaler, injectable product) are encouraged.

Where appropriate, (e.g., for parenteral products) include directions to examine the solution for product integrity before use, such as:

“Do not use this medication if it looks cloudy or is leaking.”

Heading: “Usual dose”

From the Dosage and Administration section of Part I, provide the usual dose, when to take it, how to take it, and other related details.

Heading: “Overdose”

From the Overdosage section of Part I, provide information on what to do if the individual takes too much medication. This could include overdose with a single dose or a cumulative dosing and what measures the patient should take.

The following boxed statement is to be added at the end of the narrative section. The statement may be modified to provide the most appropriate advice according to current standards of care for this drug product:

If you think you have taken too much <Brand name>, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Heading: “Missed dose”

From the Dosage and Administration section of Part I, provide information on what to do if a dose is missed. The following statements are an example of what may be used:

If you missed a dose of this medication, take it as soon as you remember. But if it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Go back to the regular dosing schedule. Do not take two doses at the same time.

or

If you missed a dose of this medication, you do not need to make up the missed dose. Skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time.

For antibiotics:

If you missed a dose of this medication, take it as soon as you remember. This will help to keep a constant amount of medication in your blood. But, if it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time.

5.5.7 Side Effects

Heading: “What are possible side effects from using <Brand name>?”

This section should include a brief summary of the self-limiting and serious side effects and the action patients should take when experiencing them. The information to be included will be determined in consultation with the sponsor and Health Canada.

The following or similar statement should be included at the beginning of the side effects section:

These are not all the possible side effects you may feel when taking <Brand Name>. If you experience any side effects not listed here, contact your healthcare professional.

Text

Self-limiting side effects should be described in narrative format. Self-limiting side effects are considered to be those that generally don't require medical attention and will usually go away as the body adjusts to the drug. In cases where this may not be easily understood or predictable, a statement may be added to help the patient understand what course of action they should take. The effects should be grouped by frequency using the terminology provided by the Council for International Organizations of Medical Sciences (CIOMS) (e.g., common, rare, etc.). A statement of the risk of dependency, if applicable, should be included here.

Table

All serious side effects should be included in the table. They do not need to be repeated in the text, as duplication generally is not wanted in Part III. Whether the patient can do something about the effect should be used as the criteria for including side effects in the table. The term ‘serious side effects’ is one that is easily understood by the patient and does not adhere to any international guideline or standard definition of ‘serious adverse event’. The side effects should be grouped by frequency using the CIOMS terminology. Within each group the effects should be listed alphabetically.

The table should always follow the text.

For serious side effects, instructions to discontinue the use of the product (if safe to do so) should be provided.

Footnotes should not be added to the serious side effects table.

The following or similar statement should be included after the serious side effects table:

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

5.5.8 Reporting Side Effects

A box called Reporting Side Effects should be included. See the template for wording and format.

5.5.9 Storage

Heading: “Storage”

This section should include a brief description of the storage and disposal instructions as provided in the Storage, Stability and Disposal section of Part I.

The following or similar statement should be included for all products:

Keep out of reach and sight of children.

5.5.10 More Information

Heading: “If you want more information about <Brand name>:”

For general instructions on the information contained in Part III, where to find the full product monograph and how to contact the sponsor, the manufacturer’s website and toll free number should be provided. The following or similar statement should be included:

- *Talk to your healthcare professional*
- *Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; (<http://hc-sc.gc.ca/index-eng.php>) the manufacturer’s website <www.website.document>; or, by calling 1-800-<telephone number>.*

A packaged drug product may remain in the distribution chain for some time after manufacture, depending on the expiry date and turnover at the retail level. Therefore, the revision date on Part III of the product monograph may not reflect the most recent revision of the information. The sponsor may add a statement similar to the following:

This information is current up to the time of the last revision date shown below, but more current information may be available from the manufacturer.

The only website links that can be listed are those which refer to the product monograph and Patient Medication Information. References or websites containing any information other than what has been authorized by Health Canada (i.e., approved drug product information) are unacceptable.

5.5.11 Date

When any part of the product monograph is revised, the revision date should be reflected as the “Last Revised” date in Part III. In the case where revisions are only made to Part III, the title page of the product monograph should also reflect this revision date.

6 GLOSSARY

Adverse Drug Reaction: a noxious and unintended response to a drug which occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of an organic function (Ref: C.01.001, *Food and Drug Regulations*).

The International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals For Human Use defines adverse drug reaction in both pre-approval and post-market settings, in the guideline: *Clinical Safety Data Management: Definitions and Standards For Expedited Reporting E2A*.

- in the pre-approval setting: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions;
- in the post-marketed setting: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

Adverse Event: any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. (Ref: ICH - *Clinical Safety Data Management: Definitions and Standards For Expedited Reporting E2A*).

Brand Name: with reference to a drug, the name, whether or not including the name of any manufacturer, corporation, partnership or individual, in English or French,
(a) that is assigned to the drug by its manufacturer;
(b) under which the drug is sold or advertised; and
(c) that is used to distinguish the drug (Ref: C.01.001, *Food and Drug Regulations*).

Canadian Reference Product: (a) a drug in respect of which a notice of compliance is issued pursuant to section C.08.004 and which is marketed in Canada by the innovator of the drug,

(b) a drug, acceptable to the Minister, that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable, bioavailability characteristics, where a drug in respect of which a notice of compliance has been issued pursuant to section C.08.004 cannot be used for that purpose because it is no longer marketed in Canada, or

(c) a drug, acceptable to the Minister, that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable, bioavailability characteristics, in comparison to a drug referred to in paragraph (a) (Ref: C.08.001.1, *Food and Drug Regulations*).

Clinically Significant Reactions: those reactions that affect prescribing because of their severity and consequent influence on the decision to use the drug, because it is critical for the safe use of the drug to monitor patients for them or because measures can be taken to prevent or mitigate harm. [Ref: United States Food and Drug Administration (FDA)].

Common Adverse Drug Reaction: an adverse drug reaction with a frequency of $\geq 1/100$ and $< 1/10$ ($\geq 1\%$ and $< 10\%$). [Ref: Council for International Organizations of Medical Science (CIOMS) convention].

Common Name: with reference to a drug, the name in English or French by which the drug is (a) commonly known; and (b) designated in scientific or technical journals, other than the publications referred to in Schedule B to the Act [e.g., United States Adopted Name (USAN), British Approved Name (BAN), International Nonproprietary Name (INN), etc.] (Ref: C.01.001, *Food and Drug Regulations*).

Crossover Study: different therapies are tested in the same individual; therefore, subjects act as their own control.

Dosage Form: a pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients (Ref: ICH Q1A).

Drug Product: the dosage form in the final immediate packaging intended for marketing (Ref: ICH Q1A).

Drug Substance: the unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form (Ref: ICH Q1A).

Generic Name: see Proper Name.

Genetic Polymorphism: intersubject variability in blood concentration following drug administration observed between individuals of different ethnic groups or within the same homogenous population. For example, individuals who for genetic reasons, are either "fast" or "slow" metabolizers.

Geometric Mean: a measure of central tendency calculated by multiplying a series of numbers and taking the n^{th} root of the product, where n is the number of items in the series. The geometric mean is useful to determine "average factors". It is often used when finding an average for numbers presented as percentages.

Multicentre Study: conducted at different institutions with all the data combined into one study.

New Drug: (a) a drug that contains or consists of a substance, whether as an active or inactive ingredient, carrier, coating, excipient, menstruum or other component, that has not been sold as a drug in Canada for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that substance for use as a drug;

(b) a drug that is a combination of two or more drugs, with or without other ingredients, and that has not been sold in that combination or in the proportion in which those drugs are combined in that drug, for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that combination and proportion for use as a drug; or

(c) a drug, with respect to which the manufacturer prescribes, recommends, proposes or claims a use as a drug, or a condition of use as a drug, including dosage, route of administration, or duration of action and that has not been sold for that use or condition of use in Canada, for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that use or condition of use of that drug (Ref: C.08.001 *Food and Drug Regulations*).

Notice of Compliance: a notice issued under section C.08.004 of the *Food and Drug Regulations*.

Parallel Study: control subjects are administered a placebo or active standard therapy at the same time as other subjects are administered experimental treatment.

Perioperative: refers to the time before, during or after surgery.

Photoallergic: a delayed immunologic type of photosensitivity involving a chemical substance to which the individual has become previously sensitized and radiant energy (Ref: Dorlands).

Photosensitivity: an abnormal cutaneous response involving the interaction between photosensitizing substances and sunlight or filtered or artificial light at wave lengths of 280-400 nm. There are two main types: photoallergy and phototoxicity.

Phototoxicity: a nonimmune, chemically induced type of photosensitivity.

Pictogram: a picture like symbol used to convey a particular meaning (e.g., a non-smoking symbol).

Professed Standard: products for which no prescribed or compendial standard exists. The term refers to the label claims for quality and potency.

Proper Name: with reference to a drug, the name in English or French:

(a) assigned to the drug in section C.01.002,

(b) that appears in bold-face type for the drug in these Regulations and, where the drug is dispensed in a form other than that described in this Part the name of the dispensing form,

(c) specified in the Canadian licence in the case of drugs included in Schedule C or Schedule D to the Act, or

(d) assigned in any of the publications mentioned in Schedule B to the Act in the case of drugs not included in paragraph (a), (b) or (c) (Ref: C.01.001, *Food and Drug Regulations*).

Proprietary Name: see Brand Name.

Rare Adverse Drug Reaction: an adverse drug reaction with a frequency of $\geq 1/10,000$ and $< 1/1,000$ ($\geq 0.01\%$ and $< 0.1\%$) (Ref: CIOMS convention).

Route of Administration: indicates the part of the body on which, through which or into which the product is to be introduced (Ref: Pharmeuropa, Standard Terms, January 2000).

Serious Adverse Drug Reaction: means a noxious and unintended response to a drug that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death (Ref: C.01.001, *Food and Drug Regulations*).

A Serious Adverse Event: (experience) or reaction is any untoward medical occurrence that at any dose results in death; is life threatening (Ref: ICH - Clinical Safety Data Management: Definitions and Standards For Expedited Reporting E2A).

Subsequent Entry Product: a new drug that, in comparison with another drug, contains identical amounts of the identical medicinal ingredients, in comparable dosage forms, but that does not necessarily contain the same non-medicinal ingredients.

Uncommon Adverse Drug Reaction: an adverse drug reaction with a frequency of $\geq 1/1,000$ and $< 1/100$ ($\geq 0.1\%$ and $< 1\%$) (Ref: CIOMS convention).

Very Common Adverse Drug Reaction: an adverse drug reaction with a frequency of $\geq 1/10$ ($\geq 10\%$) (Ref: CIOMS convention).

Very Rare Adverse Drug Reaction: an adverse drug reaction with a frequency of $< 1/10,000$ ($< 0.01\%$) (Ref: CIOMS convention).

Appendix A Preparing a Product Monograph for a Product with a Notice of Compliance with Conditions

1 Introduction

The purpose of this section is to assist the sponsor in developing a product monograph for a drug product authorized under the Notice of Compliance with Conditions (NOC/c) policy and is intended to be used as a companion to the core guidance document. NOC/c products have certain unique information requirements that do not fall within the scope of the standard product monograph guidance. Except for the sections of the product monograph identified in this section, the core guidance document should be used to prepare an NOC/c product monograph.

An electronic template (in Microsoft Word[®] format) is available on the Department website for use when preparing an NOC/c product monograph.

2 Cover Page (*the following additional information is required*)

The following boxed information should be included on the cover page, after the product information, for all products authorized under the Notice of Compliance with Conditions policy:

“<Brand name>, indicated for:
- < >
*has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for <Brand name> please refer to Health Canada’s Notice of Compliance with conditions - drug products website:
<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php>”*

[For market authorizations without conditions]
“<Brand name> indicated for:
- < >
has been issued marketing authorization without conditions.”

3 General Information (*this is a new section*)

General information relating to issuance of a Notice of Compliance with Conditions (NOC/c) status should be included in the product monograph. The text should immediately follow the cover page in a format similar to that provided in the template. The first section (i.e. “What is a Notice of Compliance with Conditions (NOC/c)?”) should be repeated in Part III: Patient Medication Information, but in plain language (see section 8 of this Appendix for the text).

Boxed information:

**This product has been authorized under the
Notice of Compliance with Conditions (NOC/c)
for one or all of its indicated uses.**

Text information:

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market authorization granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol **NOC/c**. These sections may include, but are not limited to, the following:

- Indications;
- Action and Clinical Pharmacology;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Reactions associated with normal use of these and all drug products to Health Canada's Canada Vigilance Program at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

4 **Part I: Health Professional Information** (*the following additional information is required*)

The following boxed text should appear at the beginning of the section:

*"<Brand name>, indicated for:
- < >
has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for <Brand name> please refer to Health Canada's Notice of Compliance with conditions - drug products website:
<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php>"*

[For market authorizations without conditions]
*"<Brand name> indicated for:
- < >
has been issued marketing authorization without conditions."*

5 **Indications** (*the following additional information is required*)

Wording for this section must reflect that the indication, for which authorization has been granted, is based on promising information that the product may be useful in the treatment of <x>.

6 Part II: Scientific Information *(the following additional information is required)*

The following boxed text should appear at the beginning of the section:

*“<Brand name>, indicated for:
- < >
has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for <Brand name> please refer to Health Canada’s Notice of Compliance with conditions - drug products website:
<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php>”*

[For market authorizations without conditions]
*“<Brand name> indicated for:
- < >
has been issued marketing authorization without conditions.”*

7 Clinical Trials *(the following information requirements differ)*

Sponsors will complete the tabular summary of available clinical trial information upon which market authorization was granted. Details of confirmatory studies should not be provided in this section.

8 Part III: Patient Medication Information (*the following additional information is required*)

The following boxed text should appear at the beginning of the section:

“For the following indication(s) <Brand name> has been approved with conditions (NOC/c). This means it has passed Health Canada’s review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.”

[Provide a bullet listing of the indications from Part I.]

- <text>

[If the Indications section includes lifestyle recommendations as part of the therapy, they should be included here.]

“For the following indication(s) <Brand name> has been approved without conditions. This means it has passed Health Canada’s review and can be bought and sold in Canada.”

[Provide a bullet listing of the indications from Part I.]

- <text>

[If the Indications section includes lifestyle recommendations as part of the therapy, they should be included here.]

The following text must also be included:

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug’s performance after it has been sold, and to report their findings to Health Canada.

9 Presentation (*the following additional information is required*)

Each section of the product monograph for which NOC/c status requires particular attention should be identified by a **NOC/c** symbol in the left margin next to the subsection for which it applies.

Appendix B Preparing a Product Monograph for a Subsequent Entry Product (except for Schedule C and D Products)

1 Introduction

The purpose of this section is to assist the sponsor in developing a Subsequent Entry product monograph and is intended to be used as a companion to the core guidance document. Subsequent entry products have certain unique information requirements that do not fall within the scope of the standard product monograph guidance. Except for the sections of the product monograph identified in this section, the core guidance document should be used to prepare a Subsequent Entry product monograph.

An electronic template (in Microsoft Word[®] format) is available on the Department website for use when preparing a Subsequent Entry product monograph.

PART I HEALTH PROFESSIONAL INFORMATION

2 Contraindications *(the following additional information is required)*

Although a Subsequent Entry Product (except for Schedule C and D products) Monograph may not describe all dosage forms available of a particular drug, this section needs to be comprehensive to reflect all known information about the active ingredient to ensure safety.

3 Warnings and Precautions *(the following additional information is required)*

Although a Subsequent Entry Product (except for Schedule C and D products) Monograph may not describe all dosage forms available of a particular drug, this section needs to be comprehensive to reflect all known information about the active ingredient to ensure safety.

4 Adverse Reactions *(the following additional information is required)*

Although a Subsequent Entry Product (except for Schedule C and D products) Monograph may not describe all dosage forms available of a particular drug, this section needs to be comprehensive to reflect all known information about the active ingredient to ensure safety.

PART II SCIENTIFIC INFORMATION

5 Clinical Trials *(different information is required)*

The table of comparative bioavailability should be preceded by a narrative outlining the design of the study (i.e., single/multiple dose, fasting/fed, crossover/parallel, dose/number of dosing

units, number of healthy male/female volunteers/patients). The narrative on study design should include test and reference Canadian drug products.

Presentation: table (see template)

Appendix C Preparing a Product Monograph for a Schedule C Product

1 Introduction

The purpose of this section is to assist the sponsor in developing a Schedule C product monograph and is intended to be used as a companion to the core guidance document. Schedule C products have certain unique information requirements that do not fall within the scope of the standard product monograph guidance. Except for the sections of the product monograph identified in this section, the core guidance document should be used to prepare a Schedule C product monograph.

An electronic template (in Microsoft Word[®] format) is available on the Department website for use when preparing a Schedule C product monograph.

2 Presentation

In all sections and subsections, where applicable, units of radioactivity should be expressed in both International System (S.I.) of units (i.e. Becquerels) and customary Radiation Units (i.e. Curies) for the convenience of the Canadian nuclear medicine community.

PART I HEALTH PROFESSIONAL INFORMATION

3 Serious Warnings and Precautions Box

For all radiopharmaceuticals the Serious Warnings and Precautions Box should contain the following or similar statement:

Radiopharmaceuticals should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans.

4 Dosage and Administration *(new subsections are required and there are different information requirements)*

The following subsections from the standard product monograph are not required for radiopharmaceuticals:

Recommended Dose and Dosage Adjustment
Missed Dose

4.1 Dosage (*this is a new subsection*)

This subsection replaces the first paragraph under Recommended Dose and Dosage Adjustment in the core document. All other paragraphs are applicable to radiopharmaceutical products. This section should provide detailed information about the recommended dosage (amount of radioactivity to be administered) including dosage range, the optimal or usual dosage, maximum dose, and any other relevant information which may provide appropriate guidance regarding the radioactive drug usage. When appropriate, dosages should be provided for each indication. Special consideration should always be given to the appropriate dosage concerning children, patients with certain disease conditions, and other special groups.

Special instruction should be included on the clinical use (e.g., patient preparation, scanning or imaging time post-injection) especially in the case where adjunctive pharmaceuticals or techniques are required, in order to obtain the best diagnostic or therapeutic results.

Special consideration should always be given to the appropriate dosage and other management recommendations in special populations (e.g., children, elderly patients, patients with concurrent disease, and other special groups). When an age descriptor is used (e.g., children), the age range should be specified.

4.2 Administration (*the following additional information is required*)

Information concerning dilutions, delivery systems, radioactivity measurement, routes of administration of the dosage form, and specific techniques should also be included. The radioactivity content of all radiopharmaceuticals and patient doses should be measured, and the following or similar statement should be included:

The patient dose should be measured by a suitable radioactive dose calibration system prior to administration.

It is understood that there may be situations such as soft beta-emitting radioisotope labelled products, where it is not possible to measure the patient dose, and therefore the above statement is not required.

4.3 Image Acquisition and Interpretation (*this is a new subsection*)

This subsection should provide the specific requirements for image acquisition and interpretation such as type of equipment and calibration scanning or imaging time post injection, location of views, and frequency of images.

4.4 Instructions for Preparation and Use (*this is a new subsection*)

This subsection should contain detailed instructions on the preparation of radiopharmaceuticals from kits and instructions for elution process from Generators. The following or similar statement should be included:

The components of the reagent vial are sterile and nonpyrogenic. It is essential that the user follows the directions carefully and adheres to strict aseptic technique.

Use aseptic technique and wear waterproof gloves throughout the entire preparation procedure.

Make all transfers of radioactive solutions with an adequately shielded syringe and maintain adequate shielding around the vial during the useful life of the radioactive product.

4.5 Directions for Quality Control (*this is a new subsection*)

This subsection should contain information required for quality control of the radiopharmaceutical product. The following or similar statement should be included:

The appearance, pH and radiochemical purity of the radiopharmaceutical product should be determined prior to administration to the patient.

The manufacturer's specification for appearance, pH, radiochemical purity, chemical/radiochemical impurity, total radioactivity, specific activity, radioactive concentration, osmolality, particle size, if applicable, should be stated in this subsection. Suggested methodologies should be provided to ensure quality control results.

5 Radiation Dosimetry (*this is a new section*)

This section should contain established radiation dose estimates absorbed by organs/tissues of an average adult human after the administration of the recommended amount (activity) of the radiopharmaceutical. The route of administration should be specified and the data presented in tabular format. All target organs and organs at risk should be included. Absorbed radiation dose estimates should be expressed in mGy/MBq (rad/mCi) per unit activity injected and/or per maximum recommended dose. The method of calculation (including parameters and models) should be specified. Dose estimates from any radiocontaminant should be provided either as a separate dose or expressed as a percentage of total dose estimates. The Effective Dose Equivalent (E.D.E) and/or the Effective Dose (E.D.) expressed as mSv/MBq (rem/mCi) should be included in the table of dose estimates.

Final Dose Estimated (the model and method of calculation should be specified).

Presentation: table (see template)

6 Description (*this is a new section*)

This section should contain a brief description of the physical characteristics and external radiation for the radioisotope already present in the final product, or to be used in reconstitution process. For Generators, it should be for both the parent and the daughter radionuclides. Further and more detailed information (e.g., pH, particle size) should appear in the Pharmaceutical Information section.

6.1 Physical Characteristics

This subsection should include physical half-life, principle radiation emission data and physical decay chart (in tabular format). For Generators the physical characteristics data for both the parent and the daughter radionuclides should be provided.

6.2 External Radiation

This subsection should include the specific gamma ray constant for the radioisotope, and the radiation attenuation by lead shielding (in tabular format). For Generators, the physical decay chart for both the parent and the daughter radionuclides should be included.

7 Warnings and Precautions (*the following additional information is required*)

7.1 General

For all radiopharmaceutical products a statement about the special restrictions for use should be provided to complement the information contained in the warning box. The following or similar statements should be included for all radiopharmaceuticals:

The product should be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

The radiopharmaceutical product may be received, used and administered only by authorized persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of local competent official organizations.

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

For radiopharmaceutical kits the limitations of use should be provided. The following or similar statements should be included:

The contents of this kit are intended for use in the preparation of <product> and are not to be directly administered to the patient.

The contents of the kit are not radioactive. However, following the addition of radionuclide (e.g., Tc 99m, In-111, Y-90, etc.), adequate shielding of the final preparation should be maintained to minimize radiation exposure to occupational workers and patients.

For kits used in preparation of Tc 99m radiopharmaceuticals the following or similar statement should be included:

The Tc 99m labelling reactions involved depend on maintaining the tin (stannous ion) in the reduced state. Hence, sodium pertechnetate Tc 99m containing oxidants should not be employed.

7.2 Contamination *(this is a new subsection)*

This subsection should contain practical information for the patient to minimize the contamination potential after receiving the drug. This information must also appear in Part III - Patient Medication Information. The following information should be provided to the patient when applicable:

The following measures should be taken for up to 12 hours after receiving the radiopharmaceutical product: Toilet should be used instead of urinal. Toilet should be flushed several times after use. If blood or urine gets onto clothing such clothing should be washed separately or stored for 1 to 2 weeks to allow for decay.

Special precautions such as bladder catheterization should be taken following administration to incontinent patients to minimize the risk of radioactive contamination of clothing, bed linen and the patient's environment.

7.3 Pregnant Women (*the following additional information is required*)

The following or similar statement should be included for all radiopharmaceutical products:

Ideally, examinations using radiopharmaceuticals, especially those elective in nature of women of childbearing capability, should be performed during the first ten days following the onset of menses, or after ensuring the woman is not pregnant. The benefit of using a diagnostic radiopharmaceutical should be weighed against the possible risk to an embryo or a fetus.

When animal reproductive studies and well controlled studies concerning fetal risk in humans are not available, an appropriate precaution should be included in this subsection, provided the investigational and post-marketing experiences have not produced evidence of risk to the fetus. For example, the following or similar statement could be used:

Since adequate reproduction studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse reactions on the fetus, this radiopharmaceutical preparation should not be administered to pregnant women unless it is considered that the benefits to be gained outweigh the potential hazards to the fetus.

7.4 Breast-feeding (*the following additional information is required*)

Unless studies have shown that the product is not excreted in human breast milk the following or similar statement should be included:

Where an assessment of the risk to benefit ratio suggests the use of this product in nursing mothers, formula feeding should be substituted for breast feeding.

8 Storage, Stability and Disposal (*the following additional information is required*)

In addition to the information in the core document, the following is specific to radiopharmaceuticals. For kits, the storage conditions and expiry for the kit and the reconstituted preparation should both be included. Lead shielding requirements should also be included (for example, a product should be stored upright in a lead shielded container at controlled room temperature).

The following or similar statement should be used:

Do not use the kit beyond the expiration date stamped on the box. After preparation the <product> should be stored at room temperature until administration, within <x> hours of radiolabelling.

9 Special Handling Instructions *(the following additional information is required)*

In addition to the information in the core document the following information is specific to radiopharmaceuticals. The following or similar statement should be used:

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

Information about management of spill or contamination should be included here.

PART II SCIENTIFIC INFORMATION

10 Product Characteristics *(this is a new section)*

This section should provide detailed information about product characteristics that are in addition to those mentioned under Description or provide a lengthier description of characteristics already briefly mentioned under Description.

11 Clinical Trials *(the following additional information is required)*

In addition to the information in the core document, the following information is specific to radiopharmaceuticals. Differences are indicated below:

- may be divided into either diagnostic or therapeutic trials;
- tables should include, but may not be limited to, imaging location, patient position, number of images, interval between images, number of images per view, scan characteristics;
- the details of the equipment used in the trial should be indicated;
- negative and positive performance characteristics;
- other relevant patient and trial characteristics.

12 Non-clinical Toxicology *(the following additional information is required)*

In addition to the information in the core document, the following or similar statements should be included, where applicable:

No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether <product name> affects fertility in males or females.

As with other radiopharmaceuticals which distribute intracellularly, there may be increased risk of chromosome damage from Auger electrons if nuclear uptake occurs.

13 PART III PATIENT MEDICATION INFORMATION

This section replaces Section 5 of the core document. All information pertaining to the preparation of a Patient Medication Information section for a radiopharmaceutical drug is provided below.

13.1 Introduction

The Patient Medication Information section is a plain language translation of information contained in Parts I and II of the product monograph. Plain language means using the simplest, most common words possible, so that information is clear, concise and easy to understand for the intended audience.

For the purposes of the product monograph, "patient" is defined as the general public. This may include an individual using the drug, a caregiver or someone who is simply interested in obtaining information about a drug.

Part III should be produced as part of the product monograph for all drugs that are required to comply with this guidance document. This applies to all drugs regardless of administration setting (e.g., hospital use only, emergency) because the ultimate audience is the general public.

The content for this section will be determined in consultation with the sponsor and Health Canada and is limited to information found in Parts I and II.

If there are other drug-specific guidelines [e.g., “*Basic Product Monograph Information for Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)*”, *Bureau of Metabolism, Oncology and Reproductive Sciences, November 2006*], this information should also be incorporated into Part III.

Where information is substantially different for each indication (e.g., diagnosis versus treatment/therapy), route of administration or formulation of the product, a separate Patient Medication Information section is warranted for each.

13.2 Language

Recognizing that there are different audiences for this information, for consistency the Patient Medication Information section should be written as if it will be read by an individual who will use or be administered the drug. For drugs where the patient is not an active participant (e.g., inhaled anaesthetics or other drugs administered under special conditions, like radiopharmaceuticals), the language may be adjusted.

Health literacy levels in Canada vary significantly among regions and demographically. For this reason, language should be adjusted for lower literacy levels. Assume that the reader has no prior knowledge of the medication or how to use it. Use the simplest, shortest words possible.

It is the responsibility of the sponsor to ensure that all translations of the Patient Medication Information section accurately reflect the meaning of the original authorized version.

In developing the Patient Medication Information section, sponsors are strongly encouraged to get help from appropriate plain language resources, including the Canadian Public Health Association and their publication *Good Medicine for Seniors: Guidelines for Plain Language and Good Design in Prescription Medication*⁸. The guidelines in this document show how to write health information in plain language for patients (for both prescription and non-prescription drugs), and include a compendium of plain language terminology. Sponsors would also benefit from user-testing their patient medication information for comprehension.

13.3 Style Guide

These style guide recommendations apply to the Product Monograph Part III as well as any patient medication information documents or leaflets that are produced as part of the drug product packaging.

- The Patient Medication Information section should not be promotional in tone or content. The text should be factual and avoid vague generalizations.
- Brand name should be used in the headings and the text.
- Page layout: left-justified.
- Margins:
 - (a) Product Monograph Part III - 2.5 centimetre (1") top, bottom and sides
 - (b) Patient Medication Information leaflet - 0.75 centimetre (0.3") top, bottom and sides
- Font:
 - (a) Product Monograph Part III - Sans Serif type fonts (e.g., Calibri 12 point, Arial 11 point);
 - (b) Patient Medication Information leaflet - Sans Serif type fonts (such as Arial or Calibri) are recommended, text - 10 point and tables - 9 point. Flexibility will be exercised in those situations where a smaller font may be necessary due to packaging

⁸ Canadian Public Health Association, 2002

constraints or printing limitations. Legibility is the goal and sponsors are responsible for ensuring that the Patient Medication Information, as it appears on the leaflet, is clear and easy to read to the patient under the customary conditions of purchase and use.

A person with normal vision, or those with corrective glasses that restore normal vision, should be able to read the information without straining. The colour, contrast, the position, and the spacing of the information are all to be taken into consideration in complying with these requirements.

- Headings and Subheadings: bold type face should be used. Italics and underlining should be avoided. All upper case font should also be avoided except where instructed (e.g., READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE, PATIENT MEDICATION INFORMATION and BRAND NAME at the beginning of the Patient Medication Information section).
- The information should be as brief and succinct as the requirements of the guidelines allow.

13.4 Readability and Usability

To ensure the Patient Medication Information section can be understood:

- Aim for a Grade 6 - 8 reading level. Tests and resources are available in libraries and on-line to ensure the readability of text such as the Flesch-Kincaid, Fry Graph Readability Formula and SMOG (Simple Measure of Gobbledygook) health literacy readability tools.
- The Patient Medication Information section should be simple, clear and easy to understand so that patients are able to find, understand and act upon the information. Consider these tips:
 - Write directly to your reader, using the first person (you, we).
 - Use clear, positive instructions (e.g., **Instead of:** Do not take this medicine on an empty stomach. **Say:** Take this medicine with food.)
 - Write instructions consecutively (i.e., in the order you want them carried out).
 - Use the shortest, most common words possible (e.g., **Instead of:** You may experience edema of the legs. **Say:** Your legs may swell.)

- Avoid acronyms, abbreviations, foreign terms and technical jargon. If you must use a technical term, define it in plain language immediately after the word.
- Use active (rather than passive) voice. Make sure the subject is named and acts on the object, and keep the subject close to the verb (e.g., **Instead of:** This medication is to be taken before every meal by your child. **Say:** Give your child this medication before every meal.).
- Where possible, use bulleted information instead of sentences and paragraphs. When sentences are necessary, keep them short with one idea in each sentence. Break up long text and remove unneeded words.
- Use minimal punctuation. If there are a lot of commas and semicolons, the sentences are likely too long.
- For long lists, use a bulleted list (instead of paragraph format).
- When using numbers, numerals are easier to read than written words (e.g., 53, instead of fifty-three). Where appropriate, include imperial equivalents in brackets after metric measurements, since many seniors and people from other countries use imperial.

13.5 Using the Template

11.5.1 General

A template of the Patient Medication Information section has been provided in Appendix H (as part of the product monograph template).

There should be a header placed on the first page of the monograph with the words in upper case, “READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE”.

At the beginning of the document, the brand name of the drug should appear in upper case, with the proper name of the drug in final dosage form in lower case appearing below the brand name. Where there is no proper name, use the common name in final dosage form. Consider adding in brackets, a phonetic spelling of the brand name or proper name. If a phonetic spelling of the brand name is included, it should be on the line preceding the brand name. If a phonetic spelling of the proper name is included, it should be on the line following the proper/common name.

When there is a boxed statement in any section of Part I or II, a corresponding boxed statement, in plain language, should appear in the relevant section of Part III.

13.5.2 Opening Disclaimer

The following or similar statement should be included for all drugs:

Read this carefully before you start taking <Brand name> and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about <Brand name>.

13.5.3 About the Medication

Heading: “What is <Brand name> used for?”

Provide a bullet listing of the indications from Part I. If the product is intended for use as an adjunct to other measures (e.g., diagnosis, treatment/therapy), this should be included.

Heading: “How does <Brand name> work?”

From the Action and Clinical Pharmacology section of Part I, and the Clinical Trials section of Part II, provide one or two sentences, explaining the mechanism of action of the drug in plain language and how it is expected to work so as to be useful in this instance (e.g., for a diagnostic radiopharmaceutical this could include note of approximate imaging times, why more than one imaging session may be required, etc. For a therapeutic radiopharmaceutical, relating the biologic behaviour of the drug—perhaps an affinity for skeletal tissue—with the desired outcome (e.g., palliation of pain) can be helpful. In some instances, attempting to describe the type of radiation and characteristics associated with the particular radioisotope component of the drug may be useful). If use of co-medications are required [e.g., potassium iodide (SSKI)], this can be noted here.

For a radiopharmaceutical drug, it is also important to note that the patient will receive a radiation dose.

Heading: “What are the ingredients in <Brand name>?”

Proper name; clearly note the radioisotope that is a component of the drug.

List non-medicinal ingredients using either proper, common or international nomenclature and in alphabetical order. A heading such as “non-medicinal ingredients” should clearly separate the non-medicinal ingredients from the radioisotope.

Heading: “Do not use <Brand name> if:”

For each situation described in the Contraindications section of Part I, include a corresponding situation in a bulleted list, in plain language, where appropriate.

13.5.4 Warnings and Precautions

This section should include serious issues/precautions associated with the use of the drug. Using as few words as possible, and where appropriate, explain the importance of a warning or precaution (i.e. why).

Serious Warnings and Precautions Box

When there is a Serious Warnings and Precautions box, it should be placed after the opening disclaimer. Only when there is a Serious Warnings and Precautions box in Part I, should a corresponding box appear in Part III.

The boxed information should contain the heading “**Serious Warnings and Precautions**” and briefly detail, in bulleted form, serious concerns associated with using this drug. The box should contain a plain language version of the same information that is provided in the Serious Warnings and Precautions Box in Part I. Adjustment of this information, if necessary, will be determined in consultation with the sponsor and Health Canada. Cross-references to other sections of Part III may be included.

A general statement regarding the specialized nature of radiopharmaceuticals (e.g., authorized persons, designated personnel, regulation and licensing by official organizations) should also be included.

Heading: “To help avoid side effects and ensure proper use, talk to your healthcare professional before you take <Brand name>. Talk about any health conditions or problems you may have, including if you:”

Enter one point for each warning and precaution from Part I in a bulleted list, in plain language.

Heading: “Other warnings you should know about:”

This section is included only when there are other general warnings and precautions that are not serious and do not fit under existing headings.

13.5.5 Interactions

Heading: “Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.”

Heading: “The following may interact with <Brand name>:”

Provide a bulleted list.

This section is to ensure patients are aware of any medications, foods (e.g. citrus, dairy), beverages (e.g., alcohol) or natural health products known to interact with this medication. Serious or significant interactions should be listed in bullet form (for example drug interactions listed in the Serious Drug Interactions box in Part I). If no relevant interactions are known, add a statement to reflect this.

For radiopharmaceutical drugs, when no interactions have been documented as known to occur, this can be noted as “No known interactions with this medication have been documented” or a similar statement.

13.5.6 Proper Use

Heading: “How to take <Brand name>:”

For radiopharmaceuticals, the following or similar statement should be used:

<Brand name> will be given to you by a healthcare professional who is experienced in the use of radiopharmaceuticals.

13.5.7 Side Effects

Heading: “What are possible side effects from using <Brand name>?”

This section should include a brief summary of the self-limiting and serious side effects and the action patients should take when experiencing them. The information to be included will be determined in consultation with the sponsor and Health Canada.

The following or similar statement should be included at the beginning of the side effects section:

These are not all the possible side effects you may feel after receiving <Brand name>. If you experience any side effects not listed here, contact your healthcare professional.

Text

Self-limiting side effects should be described in narrative format. Self-limiting side effects are considered to be those that generally don't require medical attention and will usually go away as the body adjusts to the drug. In cases where this (the self-limiting nature of the side effect) may not be easily understood or predictable, a statement may be added to help the patient understand what course of action they should take. The effects should be grouped by frequency using the terminology provided by the Council for International Organizations of Medical Sciences (CIOMS) (e.g., common, rare, etc.).

Table

All serious side effects should be included in the table. They do not need to be repeated in the text, as duplication generally is not wanted in Part III. Whether the patient can do something about the effect should be used as the criteria for including side effects in the table. The term 'serious side effects' is one that is understood by the patient and does not adhere to any international guideline or standard definition of 'serious adverse event'. The side effects should be grouped by frequency using the CIOMS terminology. Within each group the effects should be listed alphabetically.

The table should always follow the text.

For serious side effects, instructions to discontinue the use of the product (if safe to do so) should be provided.

Footnotes should not be added to the serious side effects table.

The following or similar statement should be included after the serious side effects table:

If you have a troublesome symptom or feeling that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

If the product does not have serious or important side effects, a rationale to omit the table should be provided to Health Canada.

13.5.8 Reporting Side Effects

A box called Reporting Side Effects should be included. See the template for wording and format.

13.5.9 More Information

Heading: “If you want more information about <Brand name>:”

For general instructions on the information contained in Part III, where to find the full product monograph and how to contact the sponsor, the manufacturer’s website and toll free number should be provided. The following or similar statement should be included:

- *Talk to your healthcare professional*
- *Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<http://hc-sc.gc.ca/index-eng.php>); the manufacturer’s website <www.website.document>; or, by calling 1-800- <telephone number>.*

A packaged drug product may remain in the distribution chain for some time after manufacture, depending on the expiry date and turnover at the retail level. Therefore, the revision date on Part III of the product monograph may not reflect the most recent revision of the information. The sponsor may add a statement similar to the following:

This information is current up to the time of the last revision date shown below, but more current information may be available from the manufacturer.

The only website links that can be listed are those which refer to the product monograph and Patient Medication Information. References or websites containing any information other than what has been authorized by Health Canada (i.e., approved drug product information) are unacceptable.

13.5.10 Date

When any part of the product monograph is revised, the revision date should be reflected as the “Last Revised” date in Part III. Even in the case where revisions are only made to Part III, the title page of the product monograph should also reflect this revision date.

Appendix D Preparing a Product Monograph for a Schedule D Product

1 Introduction

The purpose of this section is to assist the sponsor in developing a Schedule D product monograph and is intended to be used as a companion to the core guidance document. Schedule D products have certain unique information requirements that do not fall within the scope of the standard product monograph guidance. Except for the sections of the product monograph identified in this section, the core guidance document should be used to prepare a schedule D product monograph.

An electronic template (in Microsoft Word[®] format) is available on the Department website for use when preparing a Schedule D product monograph.

PART I HEALTH PROFESSIONAL INFORMATION

2 Indications *(the following additional information is required)*

It is beyond the scope of the product monograph to provide information on the disease targeted by the indications. But it is recognized that for vaccine products, a brief description of the disease may be useful. If this information is included it should be consistent with the Canadian Immunization Guide (see <http://www.phac-aspc.gc.ca/publicat/cig-gci/>).

3 Serious Warnings and Precautions Box *(the following additional information is required)*

In addition to the information in the core document, for biological products, where the active ingredient is derived from plasma, an indication of its inherent risks should be highlighted in the Serious Warnings and Precautions Box with reference to the more detailed information under the subheading General. The following or similar statement should also be included:

The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering to the patient (see Warnings and Precautions - General).

4 Dosage and Administration

4.1 Recommended Dose and Dosage Adjustment *(the following additional information is required)*

For vaccines, this subsection should include information on booster doses. Frequency of and intervals between booster doses should be described.

5 Description *(this is a new section)*

This section should be a general description of some of the components of the method of manufacturing with detailed information on the biologic source appearing under Product Characteristics.

For blood products, where appropriate, the description should include the following or similar statement:

This product is prepared from large pools of human plasma which may contain the causative agents of hepatitis and other viral diseases.

A cross-reference to the Warnings and Precautions section should be provided.

6 Warnings and Precautions

6.1 Specific Subheadings *(the following additional information is required)*

General: In addition to the information in the core document, for products derived from plasma, the inherent risks of the product should be explained. The following or similar statement should be used:

Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. (Include those viral reduction measures that apply to the product.) Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections.

Local Skin Reactions at Vaccination Sites: Information on local reactions to vaccination administration should be described here.

7 Adverse Reactions *(the following additional information is required)*

In addition to the information in the core document, the adverse reactions for vaccines should be broken down by age of patient and should draw out relevant Canadian clinical experience.

8 Action and Clinical Pharmacology *(the following additional information is required)*

Duration of Effect *(this is a new subsection)*

This subsection applies specifically to vaccines and should describe the duration of effect of the recommended dose (e.g., duration of detectable levels of antibodies and/or conferred immunity status). It should provide the supporting information for the dosing information, such as booster dose requirements and frequency, which is specified under Dosage.

PART II SCIENTIFIC INFORMATION

9 Pharmaceutical Information

9.1 Drug Substance *(the following additional information is required)*

In addition to the information in the core document, this subsection should include information on the pharmaceutical standard. For products expressed in international units, whenever possible, the reference standard should be specified (e.g., World Health Organisation International standard).

9.2 Product Characteristics *(this is a new subsection)*

This subsection should describe the method of manufacture. Sponsors are not expected to supply proprietary information, but they must provide enough detail to provide health professionals with an understanding of how the product is prepared.

9.3 Viral Inactivation *(this is a new subsection)*

For products derived from plasma, the viral reduction steps should be detailed. Information on the selection criteria of donors should be provided.

10 Clinical Trials *(the following additional information is required)*

In addition to the information in the core document, this section should include, specifically for vaccines, information on efficacy by class of individuals, to recognize differences in immunogenicity (e.g., by different age groups).

11 Non-clinical Toxicology *(the following additional information is required)*

In addition to the information in the core document, this section should confirm if long-term studies have been done to evaluate immunogenicity.

PART III PATIENT MEDICATION INFORMATION

12 Reporting Side Effects *(the following additional information is required)*

In addition to the information in the core document, this section should include, where appropriate, a box on reporting vaccine-associated events.