Health Canada / Santé Canada

October 1, 2003

NOTICE

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The final version of this Health Canada guidance document *Guidance for Industry: Product Monograph* is now available. Comments and suggestions received from the consultation on the draft version of the guidance were reviewed and considered in the finalization of this document.

These documents are intended to replace the guideline, Product Monographs, dated July 1989 and amended May 1990; and the Guidelines for Product Monographs and Package Inserts for Schedule C Drugs, dated October 1994.

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, Supplemental New Drug, Abbreviated New Drug, Supplemental Abbreviated New Drug Submissions, and Notifiable Changes. 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. This document will not address issues relating to the availability or dissemination/distribution of the product monograph.

A phased-in approach is being proposed to implement the Product Monograph Guidance Document and Templates.

Phase One:	On a voluntary basis, the product monograph may be submitted using the new Product Monograph Guidance Document and Templates as part of a New Drug Submission, a Supplemental New Drug Submission, or a Notifiable Changes as of date of approval. This phase would also include a case-by-case consideration for submissions waiting in queue to be picked up for review.
Phase Two:	Starting one year later, the new Product Monograph Guidance Document and Templates will officially replace existing formats for all drug submissions filed with the TPD and the BGTD.

Health Canada is working on an implementation plan for the posting of product monographs. Issues regarding the timing of such a posting, translation of the product monograph, and the number of product monographs to be posted are being considered by the Product Monograph Steering Committee. Consultations with stakeholders will be held prior to any final decisions regarding implementation of the posting of product monographs.

Canada

This and other Guidance documents are available on the **Therapeutic Products Directorate / Biologics and Genetic Therapies Directorate / Marketed Health Products Directorate Website (s)** (**http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/**). The availability of printed copies of guidance documents may be confirmed by consulting the *Guidelines and Publications Order Forms* (available on the TPD/BGTD/MHPD Website) or by contacting the Publications Coordinator[1].

Should you have any questions regarding the content of the guidance, please contact

Policy Bureau
3102C1
Therapeutic Products Directorate
Health Canada
Holland Cross
Tunney's Pasture
Ottawa, Ontario
K1A 1B9

Internet:Policy_Bureau_Enquiries@hc-sc.gc.ca

Phone: (613) 948-4623
Fax: (613) 941-1812

[1] Tel: (613) 954-6466; E-mail: publications_coordinator@hc-sc.gc.ca

Health Canada Santé Canada

GUIDANCE FOR INDUSTRY

Product Monograph

Published by authority of the
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Health Products and Food Branch
Guidance Document

Canada

Our mission is to help the people of Canada maintain and improve their health. *Health Canada*	HPFB's Mandate is to take an integrated approach to the management of the risks and benefits to health related to health products and food by: • 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. *Health Products and Food Branch*

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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.

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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, Supplemental New Drug, Abbreviated New Drug and Supplemental 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.

The first product monograph guidelines were published in 1976 and revised in 1989. The objective of this revision is to make the information more useful and accessible to health professionals and consumers. This was done through the introduction of a new design and format for the product monograph, as well as more detailed guidance on information requirements for each of the sections. The changes are intended to emphasize clinical relevance, make information easy to retrieve and provide consistency across different drugs and drug classes. This revision also includes guidance for specific drug groups: a product that has been granted a notice of compliance with conditions; a subsequent entry (bioequivalent) product; a Schedule C product; and a Schedule D product. Additionally, guidance is provided for preparing information for the consumer, a new section of the product monograph.

1.2 What Is a Product Monograph?

A product monograph is a factual, scientific document on the 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 and clinical uses. The monograph should also include contraindications, warnings, precautions, adverse reactions, drug interactions and effects on laboratory tests, symptoms and treatment of overdosage, dosage and administration, storage and stability, pharmaceutical information, dosage forms, pharmacology, toxicology, microbiology, special handling instructions, information on clinical trials, information for the consumer, references, and the dates of the initial printing and current 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. Nevertheless, it should be borne in mind that the responsibility of a health professional, when prescribing a drug, involves all the relevant facts relating to that use.

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 Supplemental New Drug Submission, an Abbreviated New Drug or a Supplemental Abbreviated New Drug Submission.

The product monograph serves as a standard against which all promotional material, or advertising distributed or sponsored by the sponsor about the drug can be compared. Without limiting its generality for use as a standard, 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, D, 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 consumer respecting the use of that product (e.g., Part III, Consumer Information).

- It establishes the limitations/ parameters for all advertising, representations, and promotional or information material distributed or otherwise sponsored 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. However, a bibliography or designated published research papers may be provided to individual health professionals on their request.

1.4.2 Prescribing Information

The information described in Part I (Health Professional Information) of the product monograph constitutes prescribing information. This portion of the product monograph 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, promotional, and advertising material, other than in the case of reminder notices.

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

1.5 When a Product Monograph is Required

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

If the New Drug Submission or Supplemental 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*, the sponsor will be advised by the Manager of the Division dealing with the submission. When the medical and technical aspects of the submission have been reviewed, the staff of the Division reviewing the submission will be available to meet with representatives of the sponsor to discuss the development of an acceptable product monograph. The investment by the sponsor of the necessary resources and scientific expertise in the preparation of an acceptable, factual, and informative product monograph will contribute greatly to an efficient and rapid review.

1.6 Revisions

A product monograph can be revised by filing an acceptable Notifiable Change or Supplemental 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 consumer 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 current product monograph 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 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 sponsored by the sponsor.

A copy of the product monograph 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.

1.8 Inquiries

The Submission Information Policy Division of the Bureau of Operational Services can assist sponsors with questions concerning the preparation and filing of a draft product monograph. The Manager of the Division of the Bureau that will be responsible for reviewing the submission should be contacted if further clarification is required.

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 monograph.
- Key information should be easy to locate.
- Information in the monographs should be presented in a consistent format to facilitate ease of retrieval, particularly in an electronic environment. This requires the standardization of terminology 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 (e.g., 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 Word Perfect 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 [..].

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 medication.

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

Part III: ***Consumer Information***
Contains information derived from Parts I and II that helps the consumer 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 consumer audience. Part III is required for all drugs, regardless of the location of use (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 and included in the draft product monograph.

- "Health professional" is the preferred term that should be used in 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, etc.
- The product monograph should be supplied to Health Canada in either official language.
- 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.

2.2 Style Guide

- Paper: 21.6 x 27.9 cm (8½ x 11") portrait orientation
- Margins: 2.5 cm (1") top, bottom and sides
- Line spacing: single
- Font: Parts I &II: Times New Roman, 12-point
  Part III: Times New Roman, 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
- For Parts I and II, the first use of the brand name should be followed by the proper (or common name) in parentheses. In describing the drug's actions, pharmacology, and toxicology, the proper name should be used. For the purpose of brevity, proper name will be used in these sections of the guidance document. For Part III, brand name should be used to describe the drug.
- To emphasize important information in the product monograph, bold type face should be used. Upper case font should not be used for emphasis.
- Paragraph numbering should not be used.
- If abbreviations are used in a table, a legend should be included at the bottom of table.
- References should follow the Vancouver style (see Section 4.6)

Additional style instructions are provided for Part III Consumer Information (see Section 5.2)

2.3 Title Page

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

a) the words "Product Monograph",

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 substance(s),

e) the strength(s) and dosage form(s),

f) the pharmaceutical standard (e.g., prescribed, pharmacopeial or professed), as applicable

g) the therapeutic, diagnostic or pharmacological classification and code in accordance with the World Health Organization's Anatomical Therapeutic Chemical (ATC) index,

h) the name, place of business and website of the sponsor, and, when appropriate, the name and place of business of the distributor,

i) date: for a new monograph use the date of preparation. For subsequent revisions the date of preparation will be replaced by the most current revision; and

j) the submission control number (optional).

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

Presentation: see template

2.4 Table of Contents

The product monograph should include a table of contents with page numbers.

Presentation: see template

3 PART I: HEALTH PROFESSIONAL INFORMATION

3.1 Summary Product Information

Dosage form, strength, route of administration and a qualitative, alphabetical listing of clinically relevant nonmedicinal ingredients should be presented in a summary table at the beginning of the product monograph with a cross-reference to the complete listing in the Dosage Forms, Composition and Packaging section. Clinically relevant nonmedicinal ingredients include: ethanol, gluten, lactose, sulfite and tartrazine.[2]

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)

3.2 Indications and Clinical Use

This section should contain a point-form listing of the indications, followed by a brief discussion of any relevant clinical information.

The indications to be described in this section should be based on substantial evidence of the product's efficacy and safety, derived from adequately designed and well-controlled clinical studies. Only those indications approved by Health Canada can be included.

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

When appropriate, this section should also describe the optimal use of the product, the limitations of usefulness, and pertinent details regarding the treatment outcome (e.g., smoking cessation products should be used in combination with behaviour modification).

Any special restrictions with respect to the use (e.g., specific health professionals) and/or distribution of the product (e.g., a hospital setting, ambulance), which may be required on a temporary or permanent basis, should be declared in this section. For products requiring administration by a specialized health professional or in a restricted setting, an explanation of the restrictions should be provided. The following or similar statement should be used:

[2] Repchinsky C. Compendium of Pharmaceuticals and Specialties. Canadian Pharmacists Association, 2002.

The product should be administered under the supervision of a qualified health professional who is experienced in the use of <specify the use, e.g., cancer chemotherapeutic agents> and in the management of <specify the condition e.g., patients with severe pancytopenia>. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

If there are situations where the use of this product is not therapeutically appropriate (e.g., maintenance versus acute therapy), this information should follow at the end of the discussion.

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

3.2.1 Patient Subsets

3.2.1.1 Geriatrics

For indications approved for adults in general, a statement regarding use in the geriatric population should 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 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. One of the following or similar statements may be used:

Geriatrics: No data is available.

or

Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness and a brief discussion can be found in the appropriate sections (e.g., Clinical Trials, Pharmacology, Warnings and Precautions).

3.2.1.2 Pediatrics

For indications approved 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 16 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. One of the following or similar statements may be used:

Pediatrics: No data is available.

or

Evidence from clinical studies and experience suggests that use in the pediatric population is associated with differences in safety or effectiveness and a brief discussion can be found in the appropriate sections (e.g., Clinical Trials, Pharmacology, Warnings and Precautions).

Any information relating to clinical trials should be included in the Clinical Trials section of Part II: Scientific Information.

Presentation: point form (for indications) and narrative.

3.3 Contraindications

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

For contraindicated drug-drug 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:

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

Presentation: point form wherever possible

3.4 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 physician or by the patient in order to ensure safe and effective use of the drug.

3.4.1 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 the sponsor and Health Canada.

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. If there are no serious warnings, this box may be omitted.

Statement examples:

- Drug interactions with digoxin, phenytoin (see Drug Interactions section)
- Liver toxicity (see Hepatic section below)
- Should only be administered by physicians experienced with cancer chemotherapeutic drugs (see Indications and Clinical Use)

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 and Clinical Use section.

Presentation: point form within a box (see template)

3.4.2 Specific Subheadings

Subheading(s) should be used to group the information in this section. Subheadings should be ordered as presented below. Information presented within subheadings should be in order of importance.

General: This section 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 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.

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.

Neurologic

Ophthalmologic

Peri-Operative Considerations: This section 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 section.

Renal

Respiratory

Sensitivity/Resistance

Sexual Function/Reproduction

Skin: Where applicable, photosensitivity (photoallergic or phototoxic) reactions should be included.

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.

Nonteratogenic effects should be included (e.g., withdrawal symptoms, hypoglycemia). If contraindicated in pregnancy, this should be included in this section and the Contraindications section.

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

Wide: > 1000 pregnancies [3]
Limited: < 1000 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.

Nursing Women: 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.

[3] Extent of exposure categories are based on CIOMs.

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 section should contain specific monitoring and hazards associated with pediatric use of the drug. The term pediatric generally pertains to persons between birth and 16 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.

Geriatrics: This section 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.

Monitoring and Laboratory Tests: This section should include important monitoring parameters (e.g., blood pressure), 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.

3.5 Adverse Reactions

This section should contain information on all types of adverse drug reactions (ADRs) including those identified during clinical trials and as a result of post-market surveillance. Information relating to clinical trial ADRs and post-market ADRs should be presented separately.

MedDRA (Medical Dictionary for Regulatory Activities) will be used as the preferred terminology to describe adverse drug reactions. This will usually be at the Preferred Term Level, although there may be instances where the use of a Lowest Level Term or a High Level Term may be appropriate.

The standard for defining frequency terms will be based on the Council for International Organizations of Medical Science (CIOMS) convention. Specifically:

Very common: ≥ 1/10 (≥ 10%)
Common (frequent): ≥ 1/100 and <1/10 (≥ 1% and <10%)
Uncommon (infrequent): ≥ 1/1 000 and <1/100 (≥ 0.1% and <1%)
Rare: ≥ 1/10 000 and <1/1 000 (≥ 0.01% and <0.1%)
Very rare: <1/10 000 (<0.01%), including isolated reports

3.5.1 Adverse Drug Reaction Overview

The purpose of this section is to present a summary of the adverse drug reaction (ADR) information that may affect prescribing decisions or would be useful in observing, monitoring or advising patients. The information to be included will be determined in consultation with the sponsor and Health Canada. If this information is included in other sections of the product monograph (e.g, Warnings and Precautions), it should be cross-referenced here.

It should highlight the following:

- serious adverse drug reactions [4]
- the most frequent adverse drug reactions
- adverse drug reactions that most commonly result in clinical intervention (e.g., discontinuation, dose modification, concomitant medication to treat an adverse drug reaction symptom, or close monitoring), factors that may affect the rate or severity of a reaction (e.g., disease state, concomitant therapy, demographic subgroup, or dose).

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

Presentation: narrative

3.5.2 Clinical Trial Adverse Drug Reactions

General Statement

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

[4] The determination of a "serious adverse drug reaction" can be found in Guidelines to Manufacturers (rev July 2001)

Because clinical trials are conducted under very specific conditions the adverse drug 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 drug 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 drug reaction data should be preceded by a brief description of the data source. It should include overall exposure, study design, composition of control group, the basis for including adverse drug reactions in the data source, any critical exclusions and any unusual components.

Relative Frequency of Adverse Drug Reactions

- intended to display the common and very common ADRs (all ADRs with a frequency of $\geq 1\%$);
- single table preferably (multiple tables are appropriate when the drug's adverse drug reaction profile differs substantially from one population or setting to another, the different drug reactions are clearly drug-related, and the data is clinically important for use, nonuse or monitoring). Important differences may result from different product indications, formulations, population subgroups, study durations, dosing regimens and types of studies (e.g., intensely monitored versus a large outcome study);
- data in the primary table should be derived from placebo-controlled trials. If this is not available or not informative, the primary table should be based on active-controlled data;
- elaboration of tabular data: the data table should be followed by a narrative discussion to explain or supplement the information provided in the table. Where possible, it should include the following:

    - ***Dose-response information***: identify adverse drug reactions that exhibit a dose-response and describe the manner in which dose-response was investigated.

    - ***Special Populations:*** information about observed differences in adverse drug reaction rates in various demographic groups or disease subsets. Where no information about special populations is available, this should be stated and an explanation provided.
    - Information on dosage and duration of therapy linked to adverse drug reactions.

- ***Pooling Data***: Data from different studies should be pooled to provide a single table of adverse drug reaction rates, unless there are major study-to-study differences.

- ***Body System Organization***: Information should be categorized alphabetically by organ system in accordance with the organ classes proposed by MedDRA. Within each organ class the adverse drug reactions will be presented by decreasing frequency. Additionally the terms used to describe the adverse drug reactions should be in accordance with those proposed by MedDRA.

- ***Denominator***: The denominator (n= number of patients) should be provided for each column in the table.

- ***Percentages***: Adverse drug reaction rates should generally be rounded off to the nearest integer. An exception would be for particularly serious adverse drug reactions occurring at low rates in a large study where fractions of a percent may be meaningful.
- Graphs should not be used to present ADR information.

Presentation: table and narrative (see template)

3.5.3 Less Common Clinical Trial Adverse Drug Reactions

Clinical trial adverse drug reactions with a frequency cut off of <1% should be presented as a listing and categorized by body system.

Presentation: list

3.5.4 Abnormal Hematologic and Clinical Chemistry Findings

Clinically significant changes in laboratory values identified during clinical trials should be summarized in table format. Where applicable, there should be one table for hematologic changes and one for chemistry changes. 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 it should also provide the number of patients that met the criteria. It would also be useful to provide a normal range for each laboratory parameter.

Presentation: table

3.5.5 Post-Market Adverse Drug Reactions

In this section all post-market adverse drug reactions (e.g., Canadian and international) should be included in this section. It should include serious and unexpected ADRs that are reported through post-market surveillance and identified in Phase IV clinical trials.

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

3.6 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.

3.6.1 Serious Drug Interactions Box

Serious life threatening interactions should be included here (i.e., 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 Warnings 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: point form within a box (see template)

3.6.2 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 text 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 section 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

3.6.3 Drug-Drug Interactions

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

Pharmacokinetic studies presenting information regarding the kinetics of specific drug combinations should be presented in Part II: Detailed Pharmacology. However, a summary statement drawn from the pharmacokinetic information should be presented in the Drug Interactions section.

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 text format. The table should include the proper name of the drug, the level 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.

3.6.4 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. 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: table format. See section 3.7.3 for additional instructions.

3.6.5 Drug-Herb Interactions

This subsection should briefly present known interactions with herbal products and practical guidance for the health professional. Tabular format is preferred, however, if data is limited, text format is acceptable.

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

Interactions with herbal products have not been established.

Presentation: table format. See section 3.7.3 for additional instructions.

3.6.6 Drug-Laboratory Test Interactions

This subsection should briefly present, in text format, 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: table format. See section 3.7.3 for additional instructions.

3.6.7 Drug-Lifestyle Interactions

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

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

3.7 Dosage and Administration

3.7.1 Dosing Considerations

This section 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: point form

3.7.2 Recommended Dose and Dosage Adjustment

This section should provide detailed and practical information on the recommended dosage. The section 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 (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), the age range should be specified. 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).

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

3.7.3 Missed Dose

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

Presentation: narrative

3.7.4 Administration

This section 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.

Use in combination with other drugs (e.g., in same I.V. 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.

Presentation: narrative

3.7.4.1 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 conditions of storage and recommended storage period of reconstituted solutions should be stated.

Presentation: narrative

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 mL

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 compatible, and the method of preparing the dilutions, should be listed.

The recommended storage period and conditions for each solution should be stated (see section 3.10)..

Presentation: table and narrative (see template)

3.8 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

3.9 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 pharmacology or pharmacodynamics of the drug in humans.

3.9.1 Mechanism of Action

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

3.9.2 Pharmacodynamics

This section should a brief description of factors that may affect pharmacodynamic response (clinical effectiveness, safety, and dose-response).

3.9.3 Pharmacokinetics

A summary table of the most clinically significant pharmacokinetic features should be presented in a table (see template). This section should also include a short explanation of the clinical significance of the basic pharmacokinetic data for the general population, under the following headings:

Absorption: information characterizing the drug's properties, such as area under the curve (AUC), time of maximum observed concentration (t_{max}), maximum observed concentration (C_{max}), time of onset of action, food effect on absorption (even if negligible) and time to steady state;

Distribution: degree of protein binding, extent of distribution (Vd), sites of distribution, including whether the drug crosses the blood-brain barrier;

Metabolism: sites and pathway of metabolism (e.g., p-glycoprotein, cytrochrome P450) and extent of first-pass metabolism, biological/pharmacological activity of metabolites, dose dependent changes in metabolism;

Excretion: route(s) and the percentage attributable to each route, elimination half-life ($t_{1/2}$), clearance.

This section should provide 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.

3.9.3.1 Special Populations and Conditions

This section should include pharmacokinetic information that is relevant to special populations (e.g., pediatrics, geriatrics, gender, genetic polymorphism, race) and certain conditions (e.g., hepatic insufficiency, renal insufficiency).

Information about pharmacokinetic drug-drug interactions and information derived from animal or in vitro studies should be included in Part II: Scientific Information in the Detailed Pharmacology section. When substantial evidence exists to indicate that such information is relevant to the therapeutic use of the drug, this information should be included in the Drug Interactions section.

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

3.10 Storage and Stability

This subsection 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, it is recommended that the storage period for parenteral products normally not exceed 24 hours at room temperature (15 - 30 °C) and 72 hours under refrigeration (2 - 8 °C).

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

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 in a safe place out of the reach of children.

Presentation: narrative

3.11 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 cytotoxic drugs that may be mutagenic. When necessary, special instructions should be included for the decontamination and safe disposal of drugs and associated material.

Presentation: narrative

3.12 Dosage Forms, Composition and Packaging

This section should describe all available marketed dosage forms (with a complete physical description of each, including identifiable markings), the strength of each in terms of the concentration of medicinal ingredient, and recommended routes of administration. Other items such as those required for administration or quality control, reconstitution, elution etc. should also be included. The terminology for the routes and forms will be in accordance with those published by Health Canada.

For each strength of each dosage form of the product, the sponsor should provide an alphabetical listing of **all** nonmedicinal ingredients, using the proper or common name (i.e., not trade names).

Where applicable, components making up the capsule shell, coating, patch, etc should be also listed for each strength of each dosage form. 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 available marketing packaging formats should be included (e.g., "available in bottles of 100's, 500's, and 1000's and in blister packs of 100's"). Any additional packaging information that may impact on patient safety (e.g., latex) should be described.

Presentation: narrative or point form

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 the pivotal studies in support of the drug's efficacy and safety. The detailed information should address the following major components: the demographics of the studies, including number of study subjects (intent to treat population), age (mean and range), gender and race composition; the trial design, including dose, route of administration and duration of treatment; the results of the studies, including primary endpoints and associated values for the drug and placebo or active control and statistical significance.

The studies should be annotated to a reference to allow users of the product monograph to seek out detailed information as required. The information on clinical trials should be presented in a tabular format for ease of retrieval of the information. The demographic 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

Study Demographics and Trial design

- The description of demographic characteristics of the study population (e.g., age, gender, race, weight) and other (e.g., renal or hepatic function) subgroups should be specified so that possible differences in efficacy or safety can be identified. All subjects assigned to the treatments should be accounted for. The sample size should be based on statistical power analysis.
- The study design should be described (e.g., parallel, crossover, factorial and multicentre.)
- Studies that should be included are adequate, well-controlled 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 unapproved indication; imply comparative efficacy or parity, unless deemed pivotal by Health Canada upon issuance of a NOC for a relevant NDS or SNDS; present the incidence, frequency, severity of adverse reactions and are not the subject of an acceptable NDS, SNDS or NC submission, or at the request of Health Canada.
- Generally, recognized control groups (comparator) are placebo and/or active comparator concurrent controlled, no treatment concurrent control, active treatment concurrent control, dose comparison concurrent control, and historical control. Inclusion of placebo-controlled trials are encouraged.
- The doses or dose ranges used in the study as well as therapy duration should be provided for all treatment involved in the study.

Study Results

The primary and secondary measurements and endpoints to determine efficacy and/or safety should be clearly specified. The treatment groups should be compared for all critical measures of efficacy/safety provided. The results should show the difference between the treatment groups and the associated *p* value and/or confidence index. Results of clinical and statistical significance should be included; results that only demonstrate statistical significance without clinical significance generally should not be included, unless deemed appropriate in certain circumstances.

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

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 Detailed Pharmacology

This section should include animal data and human data, each further divided into *in vitro* and *in vivo* subsections. Each study to be included should be individually described and should provide sufficient detail to yield a meaningful interpretation. Animal data need be included only where human studies are lacking or deficient, or where the information is relevant to interpretation of toxicity or mode of action.

Within the human and animal sections, studies should be presented under pharmacodynamics and pharmacokinetics. The experiments described under pharmacokinetics are those performed using various dose levels and regimens to determine such factors as: absorption, bioavailability and bioequivalence, blood and tissue levels, distribution parameters, and binding to biological tissues. The metabolites, the concentration of metabolites, the rate of metabolism, and evidence of enzyme induction or saturation should be described, when this information is available. Also included should be the routes and manner of excretion, giving values for drug levels in bile, feces and urine, etc. Such data are best presented in tables and figures.

Factors that influence the pharmacodynamic, and pharmacokinetic profile should be described, including the effects of age, gender, pregnancy, genetic factors, disease, presence of food, pH of gastric contents, and drug interactions. The way in which pharmacokinetic factors relate to dosage, therapeutic activity, toxicity, and specific disease or physiological circumstances should be explained and referenced to statements in other sections of the product monograph.

Speculative inferences drawn from pharmacological data relating to clinical use should be made only where they concern a possible hazard.

Pivotal efficacy clinical studies should be included in the Clinical Trials section.

Presentation: table format where possible and narrative (see template)

4.4 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 comprehensive description of the microbiological data summarized under Action and Clinical Pharmacology

Details regarding susceptibility testing, reference pathogens studied and the National Committee for Clinical Laboratory Standards (NCCLS) should be included. Information on drug resistance and cross-resistance should be included.

4.5 Toxicology

This section includes special tolerance studies in humans and toxicity studies in animals, suitably subdivided. The animal studies should provide information respecting the animal species, route, form, and dosage regimen used, and a concise description of each study and the abnormal findings. Normally, a single dose study, short- and long-term multidose studies, reproductive studies, and various special studies should be included under appropriate subheadings.

This section should confirm if long-term animal studies have been done to evaluate carcinogenic or cocarcinogenic potential. When studies are available, animal species and results should be described.

This section should confirm if animal reproductive studies have been done to evaluate mutagenesis potential. When studies are available, animal species and results should be described. When there is evidence of mutagenesis, the significance of the results should be provided in the Warnings and Precautions section.

Presentation: Table format wherever possible

4.6 References

This section should include a selection of the pivotal clinical studies that formed the basis for the evaluation of the drug and the studies highlighted in the Clinical Trial section. This section may also include references to the best published papers containing preclinical data on the drug and selected, authoritative papers concerning the use of the drug. The citations should follow the Vancouver style [5]. These references should be numbered to refer to identified statements in the text of the product monograph.

Studies in support of the clinical trial section should be included (published or unpublished).

Presentation: numbered list

[5] Uniform Requirements for Manuscripts Submitted to Biomedical Journals. International Committee of Journal Editors. CMAJ 1994;150(2):147-54. Available at www.cmaj.ca/misc/ifora.shtml.

5 PART III: CONSUMER INFORMATION

5.1 Introduction

Consumer Information is a lay-language translation of information contained in Parts I and II of the product monograph.

For the purposes of the product monograph, "consumer" is defined as the general public. It 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 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 Minimum information for the Consumer Taking Non-steroidal Anti-inflammatory Drugs", Bureau of Pharmaceutical Assessment, Endocrinology, Metabolism and Allergy Division, October 1996*), this information must 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 Consumer Information section is warranted for each. For example, a product that is indicated for migraine and hypertension would have two Consumer Information sections.

5.2 Language

Recognizing that there are different audiences for this information, for consistency the section should be written in a language that is appropriate for an individual who will use or be administered the drug. For drugs where the consumer is not an active participant (e.g., inhaled anaesthetics; other drugs administered under special conditions– i.e., radiopharmaceuticals), the language should be adjusted.

It is the responsibility of the sponsor to ensure that any translations of the Consumer Information section accurately reflect the meaning of the original approved version.

In developing the Consumer Information section, sponsors may wish to seek assistance from the Canadian Public Health Association and their publication "Good Medicine for Seniors: Guidelines for Plain Language and Good Design in Prescription Medication"[6].

5.3 Style Guide

- The Consumer 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: 2 column format
- Headings: a black box with white, bold, capitalized text. Subheadings should be in bold type and/or underlined.
- The information should be as brief and succinct as the requirements of the guidelines allow, preferably no more than 2 pages
- Margins: 0.75 cm top, bottom and sides

5.3.1 Illustrations

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

Pictograms should not be used.

5.4 Readability and Usability

To ensure the Consumer Information section can be understood:

- Sponsors should ensure that the Consumer Information section is written at no greater than a Grade 8.0 reading level. Tests and resources are available to ensure the readability of text (e.g., Flesch-Kincaid Grade Level).
- The Consumer Information section should be simple, clear and easy to understand. The sponsor may want to consider using standard methodologies to ensure consumers are able to find, understand and act upon the information.

[6] Canadian Public Health Association, 2002

5.5 Using the Template

5.5.1 General

A template of the Consumer Information section has been provided in Appendices 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, "IMPORTANT: PLEASE READ"

The brand name of the drug in upper case with the proper name of the drug in lower case in brackets below the brand name should be placed at the beginning of the document.

5.5.2 Opening Disclaimer

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

> *This leaflet is part III of a three-part "Product Monograph" published when <brand name> was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about <brand name>. Contact your doctor or pharmacist if you have any questions about the drug.*

5.5.3 About This Medication

This section should include the following subsections:

What the medication is used for

From the Indications section of Part I, provide a point form listing. If the Indications section includes lifestyle recommendations as part of the therapy (e.g., diet as adjunctive therapy for antidiabetic drugs) it should be included here.

What it does

From the Action and Clinical Pharmacology section of Part I, provide a brief lay explanation of the mechanism of action of the drug. 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 one knows if it is working (e.g., improved symptomatology).

When it should not be used

From the Contraindications section of Part I, provide a point form listing.

What the medicinal ingredient is

proper name

What the important nonmedicinal ingredients are

A alphabetical listing of the nonmedicinal ingredients, as provided in the Summary Product Information section of Part I.

What dosage form it comes in

From the Dosage Forms, 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 mg, 20 mg, 100 mg)

5.5.4 Warnings and Precautions

This section should include serious issues/precautions associated with the use of the drug.

Serious Warnings and Precautions Box

The boxed information should detail serious or significant public health concerns associated with using this drug. The box should contain a lay 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.

Precautions

The information should be general in nature. The following list covers the kind of potential issues that should be included and where the information can be found in Parts I and II:

Activities (Warnings and Precautions, e.g., under Occupational Hazards)

- Current conditions (Warnings and Precautions)
- Past diseases (Warnings and Precautions)

- Reproductive issues (Warnings and Precautions)
- Anticipated medical procedures (Warnings and Precautions)

5.5.5 Interactions with This Medication

This section is to ensure consumers are aware of any medications or foods or beverages (e.g., alcohol) known to interact with this medication. Serious or significant interactions should be listed (for example drug interactions listed in the Serious Drug Interactions box in Part I).

5.5.6 Proper Use of This Medication

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

Usual dose

From the Dosage and Administration section of Part I, provide the typical dose, when to take it and how to take it.

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 can take.

Missed dose

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

> *If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses.*
>
> or
>
> *If a dose of this medication is missed, it is not necessary to make up the missed dose. Skip the missed dose and continue with the next scheduled dose. Do not double doses.*

For antibiotics:

If a dose of this medication is missed, it should be taken as soon as possible. This will help to keep a constant amount of medication in the blood. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses.

5.5.7 Side Effects and What To Do About Them

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

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

Table

Serious side effects should be included in the table. Whether the patient can do something about the effect should be used as the criteria for including side effects in the table. 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.

The following or similar statement should be included at the end of the side effect section:

This is not a complete list of side effects. For any unexpected effects while taking <Brand Name>, contact your doctor or pharmacist.

5.5.8 How to Store It

This section should include a brief description of the storage instructions as provided in the Storage Instructions section of Part I.

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

> *Keep out of reach of children*.

5.5.9 Reporting Suspected Side Effects

A box on reporting suspected adverse drug reactions should be included. See the template for wording and format.

5.5.10 More Information

For general instructions on the information contained in Part III, where to find the full product monograph and how to contact the sponsor, the following or similar statement should be included:

> *This document plus the full product monograph, prepared for health professionals can be found at: http://www.website.document*
> *or by contacting the sponsor, <Sponsor Name>, at: 1-800-XXX-XXXX*

5.5.11 Date

List the last revised date of Part III of the product monograph.

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. To conform to terms used in the *Food and Drugs Act and Regulations*, this definition is slightly different from that used by the WHO. For example, the WHO definition uses the term "physiologic" rather than "organic function. (Ref: How Adverse Reaction Information on Health Products is Used, April 2002)

Adverse Event: Any untoward medical occurrence that may present during treatment with a pharmaceutical product but that does not necessarily have a causal relationship with this treatment. This is the definition used by the WHO. The definition implies that if the reporting practitioner suspects the event is related to the administration of a drug, the event is more likely an adverse drug reaction.(Ref: How Adverse Reaction Information on Health Products is Used, April 2002)

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; (marque nominative) (Ref: *Food and Drug Act and Regulations*, Part C)

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: 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: the name of the drug 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., U.S.A.N., B.A.N., I.N.N., etc) (Ref: *Food and Drug Act and Regulations*, Part C)

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 QIA).

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

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

Generic Name: see Proper Name

Genetic Polymorphism: intersubject variability in blood concentration following drug administration observed between individuals of different races, 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) 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 Act and Regulations*)

Notice of Compliance: a notice issued under section C.08.004 of the *Food and Drug Act and 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: the name of the drug substance in English or French:
(i) assigned to the drug in section C.01.002,
(ii) 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,
(iii) specified in the Canadian licence in the case of drugs included in SCHEDULE C or SCHEDULE D to the Act, or
(iv) assigned in any of the publications mentioned in SCHEDULE B to the Act in the case of drugs not included in subparagraphs (i), (ii) or (iii) of this paragraph; (nom propre) (Ref: *Food and Drug Act and Regulations*, Part C)

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: Council for International Organizations of Medical Science (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)

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 ≥1/1 000 and <1/100 (≥0.1% and <1%). (Ref: Council for International Organizations of Medical Science (CIOMS) convention.)

Very Common Adverse Drug Reaction: An adverse drug reaction with a frequency of ≥1/10 (≥10%). (Ref: Council for International Organizations of Medical Science (CIOMS) convention.)

Very Rare Adverse Drug Reaction: An adverse drug reaction with a frequency of <1/10 000 (<0.01%). (Ref: Council for International Organizations of Medical Science (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 product approved 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. The table of contents for an NOC/c product monograph will identify where additional information is required, either as a new subsection of the monograph or within an existing section, and where information may not be required.

An electronic template (in Word Perfect format) for an NOC/c monograph is provided with this guidance document and should be used when preparing a product monograph. See Appendix F.

2 Table of Contents

To assist in developing the product monograph, a sample table of contents has been provided below. It highlights sections that are required specifically for NOC/c products as well as those sections where the information requirements may differ from the standard product monograph.

Sample Table of Contents
For an NOC/c Product Monograph

† - new section for an NOC/c product monograph
* - section is in standard monograph but requirements differ for an NOC/c product monograph

Cover Page *
General Information †
Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION *
Summary Product Information
Indications and Clinical Use *
Contraindications
Warnings and Precautions
Adverse Reactions
Drug Interactions
Dosage and Administration
Overdosage
Action and Clinical Pharmacology

Storage and Stability
Special Handling Instructions
Dosage Forms, Composition and Packaging

PART II: SCIENTIFIC INFORMATION *
Pharmaceutical Information
Clinical Trials *
Detailed Pharmacology
Microbiology
Toxicology
References

PART III: CONSUMER INFORMATION*
Opening Disclaimer
About This Medication
Warnings and Precautions
Interactions With This Medication
Proper Use of This Medication
Side Effects and What To Do About Them
How to Store It
Reporting Suspected Side Effects
More information
Date

3 Cover Page *(additional information required)*

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

> *<Brand name> , indicated for <...>, has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.*

4 General Information *(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 following the cover page in a format similar to that provided in Appendix F. The first section (i.e. "What is an NOC/c") should be repeated in Part III: Consumer Information.

Boxed information:

> *<Brand name>, indicated for <...>, has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.*

Text information:

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

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

Products approved 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 and Clinical Uses;*
- *Action and Clinical Pharmacology;*
- *Warnings and Precautions;*
- *Adverse Reactions;*
- *Dosage and Administration; and*
- *Clinical Trials.*

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Health Product Safety Information Division 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.

5 Part I: Health Professional Information *(additional information 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 studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.*

6 Indications and Clinical Use *(additional information required)*

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

7 Part II: Scientific Information *(additional information 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 studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.*

8 Clinical Trials *(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.

9 Part III: Consumer Information *(additional information required)*

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

> *<Brand Name>, for use in/as <..>, has been approved with conditions, pending the results of studies to verify its clinical benefit. For more information, patients are advised to contact their health care provider.*

The following text must also be included:

> **What is a Notice of Compliance with Conditions (NOC/c)?**
>
> An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved 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.

10 Presentation *(additional information 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 numeric 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. The table of contents for a Subsequent Entry product monograph will identify where additional information is required, either as a new subsection of the monograph or within an existing section, and where information may not be required.

An electronic template (in Word Perfect format) for a Subsequent Entry Product monograph is provided with this guidance document and should be used when preparing a product monograph. See Appendix G.

2 Table of Contents

To assist in developing the product monograph, a sample table of contents has been provided below. It highlights sections that are required specifically for Subsequent Entry products as well as those sections where the information requirements may differ from the standard product monograph.

Sample Table of Contents
For a Subsequent Entry Product Monograph (except for Schedule C and D Products)

† - new section for a Subsequent Entry product (except for Schedule C and D products) monograph
* - section is in standard monograph but requirements differ for a Subsequent Entry product monograph

Title Page
Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION

Summary Product Information
Indications and Clinical Use
Contraindications *
Warnings and Precautions *
Adverse Reactions *
Drug Interactions
Overdosage
Action and Clinical Pharmacology
Storage and Stability

Special Handling Instructions
Dosage Forms, Composition and Packaging

PART II: SCIENTIFIC INFORMATION
Pharmaceutical Information
Clinical Trials *
Detailed Pharmacology
Microbiology
Toxicology
References

PART III: CONSUMER INFORMATION
Opening Disclaimer
About This Medication
Warnings and Precautions
Interactions With This Medication
Proper Use of This Medication
Side Effects and What To Do About Them
How to Store It
Reporting Suspected Side Effects
More information
Date

PART I HEALTH PROFESSIONAL INFORMATION

3 Contraindications *(additional information 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 Warnings and Precautions *(additional information 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.

5 Adverse Reactions *(additional information 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

6 Clinical Trials *(different information)*

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. The table of contents for a Schedule C product monograph will identify where additional information is required, either as a new subsection of the monograph or within an existing section, and where information may not be required.

An electronic template (in Word Perfect format) for a Schedule C monograph is provided with this guidance document and should be used when preparing a product monograph. See Appendix H.

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.

3 Table of Contents

To assist in developing the product monograph, a sample table of contents has been provided below. It highlights the sections that are required specifically for Schedule C products as well as those sections where the information requirements may differ from the standard product monograph.

Sample Table of Contents
For a Schedule C Product Monograph

† - new section for a Schedule C product monograph
* - section is in standard monograph but requirements differ for a Schedule C product monograph

Title Page
Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION
Summary Product Information
Description †
Physical Characteristics †

- External Radiation †

Indications and Clinical Use
Contraindications
Warnings and Precautions
- Serious Warnings and Precautions Box *
- General *
- Carcinogenesis and Mutagenesis
- Cardiovascular
- Contamination †
- Dependence/Tolerance
- Ear/Nose/Throat
- Endocrine and Metabolism
- Gastrointestinal
- Genitourinary
- Hematologic
- Hepatic/Biliary/Pancreatic
- Immune
- Neurologic
- Ophthalmologic
- Peri-Operative Considerations
- Psychiatric
- Renal
- Respiratory
- Sensitivity/Resistance
- Sexual Function/Reproduction
- Skin
- Special Populations
  - Pregnant Women *
  - Nursing Women *
  - Pediatrics
  - Geriatrics
- Monitoring and Laboratory Tests

Adverse Reactions
Drug Interactions
Dosage and Administration
- Dosing Considerations
- Dosage †
- Administration †
- Image Acquisition and Interpretation †
- Instructions for Preparation and Use †
- Directions for Quality Control †

Overdosage
Action and Clinical Pharmacology
Radiation Dosimetry †
Storage and Stability *
Special Handling Instructions
Dosage Forms, Composition and Packaging

PART II: SCIENTIFIC INFORMATION
- Pharmaceutical Information
  - Drug Substance
  - Product Characteristics †
- Clinical Trials *
- Detailed Pharmacology
- Microbiology
- Toxicology *
- References

PART III: CONSUMER INFORMATION *

PART I HEALTH PROFESSIONAL INFORMATION

4 Description *(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.

4.1 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.

4.2 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.

5 Warnings and Precautions *(additional information required)*

5.1 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.*

5.2 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.*

5.3 Contamination *(new section)*

The section should contain practical information for the patient to minimize the contamination potential after receiving the drug. This information must also appear in Part III - Consumer 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.*

5.4 Pregnant Women *(additional information 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.*

When animal reproductive studies and well controlled studies concerning fetal risk in humans are not available, an appropriate precaution should be included in this section, 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.*

5.5 Nursing Women *(additional information 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 women, formula feeding should be substituted for breast feeding.*

6 Dosage and Administration *(new subsections and different information requirements)*

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

Recommended Dose
Missed Dose

6.1 Dosage *(new subsection)*

This section replaces the first paragraph under Recommended Dose 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.

6.2 Administration *(additional information 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.

6.3 Image Acquisition and Interpretation *(new section)*

This section 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.

6.4 Instructions for Preparation and Use *(new section)*

This section 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.*

6.5 Directions for Quality Control *(new section)*

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

> *The radiochemical purity of the radiopharmaceutical product should be determined prior to administration to the patient.*

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

7 Radiation Dosimetry *(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)

8 Storage and Stability *(additional information 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 *(additional information 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 *(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 *(additional information 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 Toxicology *(additional information 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 CONSUMER INFORMATION

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

13.1 Introduction

Consumer Information is a lay-language translation of information contained in Parts I and II of the product monograph.

For the purposes of the product monograph, "consumer" is defined as the general public. It 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 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 Minimum information for the Consumer Taking Non-steroidal Anti-inflammatory Drugs", Bureau of Pharmaceutical Assessment, Endocrinology, Metabolism and Allergy Division, October 1996*), this information must 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 Consumer Information section is warranted for each.

13.2 Language

Recognizing that there are different audiences for this information, for consistency the section should be written in a language that is appropriate for an individual who will use or be administered the drug. For drugs where the consumer is not an active participant (e.g., inhaled anaesthetics; other drugs administered under special conditions (i.e., radiopharmaceuticals)), the language should be adjusted.

It is the responsibility of the sponsor to ensure that all translations of the Consumer Information section accurately reflect the meaning of the original approved version.

In developing the Consumer Information section, sponsors may wish to seek assistance from the Canadian Public Health Association and consult their publication "Good Medicine for Seniors: Guidelines for Plain Language and Good Design in Prescription Medication"[7].

[7] Canadian Public Health Association, 2002

13.3 Style Guide

- The Consumer 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: 2 column format
- Headings: a black box with white, bold, capitalized text. Subheadings should be in bold type and/or underlined.
- The information should be as brief and succinct as the requirements of the guidelines allow, preferably no more than 2 pages
- Margins: 0.75 cm top, bottom and sides

13.4 Readability and Usability

To ensure the Consumer Information section can be understood:

- Sponsors should ensure that the Consumer Information section is written at no greater than a Grade 8.0 reading level. Tests and resources are available to ensure the readability of text (e.g., Flesch-Kincaid Grade Level).
- The Consumer Information section should be simple, clear and easy to understand. The sponsor may want to consider using standard methodologies to ensure consumers are able to find, understand and act upon the information.

13.5 Using the Template

13.5.1 General

A template of the Consumer 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, "IMPORTANT: PLEASE READ"

The brand name of the drug in upper case with the proper name of the drug in lower case in brackets below the brand name should be placed at the beginning of the document.

13.5.2 Opening Disclaimer

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

> *This leaflet is part III of a three-part "Product Monograph" published when <brand name> was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about <brand name>. Contact your doctor or pharmacist if you have any questions about the drug.*

13.5.3 About This Medication

This section should include the following subsections:

What the medication is used for

From the Indications section of Part I, provide a point form listing. If the product is intended for use as an adjunct to other measures (e.g., diagnosis, treatment/therapy), this should be included.

What it does

From the Action and Clinical Pharmacology section of Part I, and the Clinical Trials section of Part II, provide a brief lay explanation of the mechanism of action of the drug 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., SSKI), this can be noted here.

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

When it should not be used

From the Contraindications section of Part I, provide a point form listing.

What the medicinal ingredient is

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

What the important nonmedicinal ingredients will be

A alphabetical listing of the nonmedicinal ingredients, as provided in the Summary Product Information section of Part I.

13.5.4 Warnings and Precautions

This section should include serious issues/precautions associated with the use of the drug.

Serious Warnings and Precautions Box

The boxed information should detail relevant serious or significant public health concerns associated with using this drug as per the Warnings and Precautions section in Part I. The information to be included in the box will be determined in consultation with the sponsor and Health Canada.

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.

Precautions

A listing of other warnings and precautions should follow the boxed information. The information should be general in nature. The following list covers the kind of potential issues that should be included and where the information can be found in Parts I and II:

- Current conditions (Warnings and Precautions)
- Past diseases (Warnings and Precautions)
- Reproductive issues (Warnings and Precautions)
- Anticipated medical procedures (Warnings and Precautions)
- Contamination (Warnings and Precautions)

13.5.5 Interactions with this Medication

This section is to ensure consumers are aware of any medications or foods or beverages (e.g., alcohol) known to interact with this medication. Serious or significant interactions should be listed (for example drug interactions listed in the Serious Drug Interactions box in Part I).

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 of This Medication

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

> *This <brand name> is not self-administered by an individual. It should be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals.*

13.5.7 Side Effects and What To Do About Them

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

Text

Common 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. 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

Serious and important side effects should be included in the table. Whether the patient can do something about the effect should be used as the criteria for including side effects in the table. 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.

The following or similar statement should be included at the end of the side effect section:

> *This is not a complete list of side effects. If you have any unexpected effects after receiving <Brand Name>, contact your doctor or pharmacist.*

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 Suspected Side Effects

A box on reporting suspected adverse drug reactions should be included. See the template for wording and format.

13.5.9 More Information

For general instructions on the information contained in Part III, where to find the full product monograph and how to contact the sponsor, the following or similar statement should be included:

> *This document plus the full product monograph, prepared for health professionals can be found at:* ***http://www.website.document****.*
> *or by contacting the sponsor, <Sponsor Name>, at: 1-800-XXX-XXXX*

13.5.10 Date

List the last revised date of Part III of the product monograph. It must match the date on the title page of the product monograph.

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. The table of contents for a Schedule D product monograph will identify where additional information is required, either as a new subsection of the monograph or within an existing section, and where information may not be required.

An electronic template (in Word Perfect format) for a Schedule D monograph is provided with this guidance document and should be used when preparing a product monograph. See Appendix I.

2 Table of Contents

To assist in developing the product monograph, a sample table of contents has been provided below. It highlights sections that are required specifically for Schedule D products as well as those sections where the information requirements may differ from the standard product monograph.

Sample Table of Contents
For a Schedule D Product Monograph

† - new section for a Schedule D product monograph
* - section is in standard monograph but requirements differ for a Schedule D product monograph

Title Page
Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION
- Summary Product Information
- Description †
- Indications and Clinical Use*
- Contraindications
- Warnings and Precautions
  - Serious Warnings and Precautions Box *
  - General *
  - Carcinogenesis and Mutagenesis
  - Cardiovascular
  - Dependence/Tolerance

- Ear/Nose/Throat
- Endocrine and Metabolism
- Gastrointestinal
- Genitourinary
- Hematologic
- Hepatic/Biliary/Pancreatic
- Immune
- Local Skin Reactions at Vaccination Sites †
- Neurologic
- Peri-operative Considerations
- Psychiatric
- Renal
- Respiratory
- Sensitivity/Resistance
- Sexual Function/Reproduction
- Skin
- Special Populations
- Monitoring and Laboratory Tests

Adverse Reactions *
Drug Interactions
Dosage and Administration
- Dosing Considerations
- Recommended Dose *
- Missed Dose
- Administration

Overdosage
Action and Clinical Pharmacology
- Pharmacokinetics
- Special Populations and Conditions
- Duration of Effect †

Storage and Stability
Special Handling Instructions
Dosage Forms, Composition and Packaging

PART II: SCIENTIFIC INFORMATION

Pharmaceutical Information
- Drug Substance *
- Product Characteristics †
- Viral Inactivation †

Clinical Trials *
Detailed Pharmacology *
Microbiology
Toxicology *
References

PART III: CONSUMER INFORMATION

Opening Disclaimer
About This Medication
Warnings and Precautions

Interactions With This Medication
Proper Use of This Medication
Side Effects and What To Do About Them
How to Store It
Reporting Suspected Side Effects *
More information
Date

PART I HEALTH PROFESSIONAL INFORMATION

3 Description *(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 Warmings section should be provided.

4 Indications and Clinical Use *(additional information required)*

It is beyond the scope of this section 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 www.hc-sc.gc.ca/hpb/lcdc/publicat/immguide/index.html).

5 Warnings and Precautions

5.1 Serious Warnings and Precautions Box *(additional information 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 -General).*

5.2 Specific Subheadings *(additional information 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.

6 Duration of Effect *(new section)*

This section applies specifically to vaccines and should describe the duration of effect of the recommended dose (for 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. More detailed information on the duration of the immune status should be provided in Detailed Pharmacology.

7 Adverse Drug Reactions *(additional information 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 Dosage and Administration

8.1 Recommended Dose *(additional information required)*

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

PART II SCIENTIFIC INFORMATION

9 Pharmaceutical Information

9.1 Drug Substance *(additional information required)*

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

9.2 Product Characteristics *(new section)*

This section 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 *(new section)*

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 *(additional information 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, for e.g. by different age groups.

11 Detailed Pharmacology *(additional information required)*

In addition to the information in the core document, for vaccines this section should include data on duration of immune status.

12 Toxicology *(additional information 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 CONSUMER INFORMATION

13 Reporting Suspected Adverse Drug Reactions *(additional information required)*

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