Health Canada Santé Canada

October 30, 2006

**NOTICE**

06-120828-643

**Release of *Draft Guidance Document for Industry, Reporting Adverse Reactions to Marketed Health Products* for Comment**

This Draft Guidance Document is intended to replace and supercede the 1996 *Guidelines for the Canadian Pharmaceutical Industry on Reporting Adverse Reactions to Marketed Drugs (Vaccines Excluded)* and its 2001 revision. It is meant to clearly and consistently communicate Health Canada's expectations concerning the reporting of adverse reactions to marketed health products by market authorization holders with respect to the *Food and Drug Regulations* and the *Natural Health Products Regulations*.

Should you wish to provide comments on this Draft Guidance Document, you are requested to do so by **December 29, 2006**. The Draft Guidance Document will be amended where applicable as a result of this consultation exercise and subsequent deliberations within Health Canada. Your comments and questions should be directed to:

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Canada

# DRAFT GUIDANCE DOCUMENT FOR INDUSTRY

## Reporting Adverse Reactions to Marketed Health Products*

* Marketed Health Products covered by this Guidance Document are listed in Section 1.1 Scope and exclude preventative immunization vaccines, blood, blood components, cells, tissues and organs, and medical devices.

**This guidance document is being distributed for comment purposes only.**

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**Health Products and Food Branch**
**Guidance Document**

Canada

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| Our mission is to help the people of Canada maintain and improve their health.<br>*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:<br>• Minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and,<br>• Promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.<br>*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 governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

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 Scope

Adverse reaction (AR) reports for the products noted below fall within the scope of this Guidance document and are to be reported to the Marketed Health Products Safety and Effectiveness Information Bureau (MHPSEIB), of the Marketed Health Products Directorate (MHPD) of Health Canada. The MHPD collects AR reports for the following marketed health products approved for use in humans:

- pharmaceutical drugs (which includes prescription and non-prescription pharmaceutical drugs);
- biologics as set out in Schedule D to the *Food and Drugs Act* (which include biotechnology products, therapeutic and diagnostic vaccines and fractionated blood products), but excluding blood and blood components and preventative immunization vaccines;
- radiopharmaceutical drugs set out in Schedule C to the *Food and Drugs Act*; and
- natural health products as defined in Section 1 of the *Natural Health Products Regulations*.

Note that drugs and natural health products authorized for clinical trials involving human subjects pursuant to Part C, Division 5 of the *Food and Drug Regulations* and Part 4 of the *Natural Health Products Regulations*, respectively, are not within the scope of this Guidance document.

In addition to the AR reports required to be reported in accordance with the *Food and Drugs Act*, the *Food and Drug Regulations* and the *Natural Health Products Regulations* (collectively these two sets of regulations are referred to hereafter as "the Regulations"), Health Canada has powers to request additional information on ARs as set out in the Regulations[1, 2, 3].

Other parts of Health Canada and certain Health Canada partners collect AR reports on other products. Appendix 5 provides further details on these other reporting programs.

## 1.2 Definitions

Definitions for a number of terms used in this document are set out below. A complete Glossary is included in Appendix 1.

"**Adverse reaction (AR)**" for the purpose of this Guidance document means a noxious and unintended response to a marketed health product covered by this document and includes "adverse drug reaction" as defined in the *Food and Drug Regulations*[4] and "adverse reaction" as defined in the *Natural Health Products Regulations*[5].

> "Adverse drug reaction" as defined in the *Food and Drug Regulations*[4] means 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.
>
> "Adverse reaction" as defined in the *Natural Health Products Regulations*[5] means a noxious and unintended response to a natural health product that occurs at any dose used or tested for the diagnosis, treatment or prevention of a disease or for modifying an organic function.

"**Serious adverse reaction**" for the purpose of this Guidance Document means a noxious and unintended response to a marketed health product covered by this document that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, that causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death and includes "serious adverse drug reaction" as defined in the *Food and Drug Regulations*[4] and "serious adverse reaction" as defined in the *Natural Health Products Regulations*[5].

> "Serious adverse drug reaction" as defined in the *Food and Drug Regulations*[4] means a noxious and unintended response to a drug that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death.
>
> "Serious adverse reaction" as defined in the *Natural Health Products Regulations*[5] means a noxious and unintended response to a natural health product that occurs at any dose and that requires in-patient hospitalization or a prolongation of existing hospitalization, that causes congenital malformation, that results in persistent or significant disability or incapacity, that is life threatening or that results in death.

"**Health product**" for the purpose of this Guidance document includes drugs, medical devices, and natural health products. Drugs include both prescription and nonprescription pharmaceuticals; biotechnology products and biologically-derived products such as vaccines, serums, and blood derived products; cells, tissues and organs; disinfectants; and radiopharmaceuticals. Note however, as set out in Section 1.1, that only some of these health products fall within the scope of the AR reporting covered by this Guidance Document.

> "Drug" as defined in the *Food and Drugs Act*[6] includes any substance or mixture of substances manufactured, sold or represented for use in:
>
> a. the diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical state, or the symptoms thereof in human beings or animals,

b. restoring, correcting or modifying organic functions in human beings or animals, or

c. disinfection in premises in which food is manufactured, prepared or kept.

"Natural health product" as defined in the *Natural Health Products Regulations*[5] is a substance set out in Schedule 1 of the *Natural Health Products Regulations* or a combination of substances in which all the medicinal ingredients are substances set out in Schedule 1 of the *Natural Health Products Regulations*, a homeopathic medicine or a traditional medicine, that is manufactured, sold or represented for use in

- the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms in humans;
- restoring or correcting organic functions in humans; or
- modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health.

However, a natural health product does not include a substance set out in Schedule 2 of the *Natural Health Products Regulations*, any combination of substances that includes a substance set out in Schedule 2 of the *Natural Health Products Regulations* or a homeopathic medicine or a traditional medicine that is or includes a substance set out in Schedule 2 of the *Natural Health Products Regulations*.

"**Market authorization holder (MAH)**" for the purpose of this Guidance document means a "manufacturer" as defined in the *Food and Drug Regulations*[7] or a licensee in the *Natural Health Products Regulations*.

"Manufacturer" or "distributor" as defined in the *Food and Drug Regulations*[7] means a person, including an association or partnership, who under their own name, or under a .trade-, design or word mark, trade name or other name, word or mark controlled by them, sells a food or drug.

## 1.3 Adverse Reaction Reporting by Market Authorization Holders

In accordance with the *Food and Drugs Act* and the Regulations[1, 2, 3], every market authorization holder (MAH) is required to report AR known to them involving their marketed health products. The success of the AR reporting system at Health Canada depends on the quality, completeness, and accuracy of the information submitted. Reporting of ARs and the monitoring thereof remain a viable means of identifying previously unrecognized rare or serious ARs . This may result in changing product safety information, facilitating decisions on regulatory actions such as withdrawal of a product from the Canadian market, contributing to international data regarding risks and effectiveness of health products, and imparting health product safety knowledge that benefits all Canadians.

In facilitating reporting of ARs by MAHs, Health Canada has harmonized to the greatest extent possible the recommendations in the International Conference on Harmonisation (ICH) guidance documents: *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*[8] (ICH E2A), *Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs*[9] (ICH E2C(R1)), and *Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting*[10] (ICH E2D), *Pharmacovigilance Planning*[11] (ICH E2E), and the Report of the Council for International Organizations of Medical Sciences (CIOMS) V Working Group: *Current Challenges in Pharmacovigilance: Pragmatic Approaches*[12].

## 1.4 Adverse Reactions

An adverse event (AE) as defined in ICH E2D[10] means any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

An AR, in contrast to an AE, is characterized by the fact that a causal relationship between the drug and the occurrence is suspected. Reportable ARs include those suspected of being the result of drug interactions (e.g., drug-drug interactions, drug-natural health product interactions, drug-food interactions).

ARs for marketed health products covered by this document may be generated from the following:

- unsolicited reporting (e.g., spontaneous reporting, scientific literature reports, stimulated reporting, active surveillance, reports via the Internet),
- solicited reporting,
- phase IV studies, and
- clinical trials where reactions are associated to a marketed comparator therapy with a labelled indication.

## 1.5 Regulations Pertaining to Adverse Reaction Reporting

The sections of the applicable regulations that set out the AR reporting requirements are listed below.

### 1.5.1 *Food and Drug Regulations*

*1.5.1.1 Adverse Drug Reaction Reporting (C.01.016, C.01.017)*

C.01.016.
(1) No manufacturer shall sell a drug unless the manufacturer, with respect to any

adverse drug reaction or any serious adverse drug reaction known to the manufacturer that occurs after this section comes into force, furnishes to the Director

(a) a report of all information in respect of any serious adverse drug reaction that has occurred in Canada with respect to the drug, within 15 days after receiving the information; and

(b) a report of all information in respect of any serious unexpected adverse drug reaction that has occurred outside Canada with respect to the drug, within 15 days after receiving the information.

(2) The manufacturer shall, on an annual basis and whenever requested to do so by the Director, conduct a concise, critical analysis of the adverse drug reactions and serious adverse drug reactions to a drug referred to in subsection (1) and prepare a summary report in respect of the reports received during the previous twelve months or received during such period of time as the Director may specify.

(3) Where, after reviewing any report furnished pursuant to subsection (1) and any available safety data relating to the drug, the Director considers that the drug may not be safe when used under the recommended conditions of use, the Director may, for the purpose of assessing the safety of the drug, request in writing, that the manufacturer submit

(a) case reports of all adverse drug reactions and serious adverse drug reactions to that drug that are known to the manufacturer; and

(b) a summary report prepared pursuant to subsection (2).

(4) The manufacturer shall submit the case reports and summary report referred to in subsection (3) within 30 days after receiving the request from the Director.

C.01.017.
The manufacturer shall maintain records of the reports and case reports referred to in section C.01.016 for auditing purposes.

*1.5.1.2 New Drugs (C.08.007, C.08.008)*

C.08.007.
Where a manufacturer has received a notice of compliance issued in respect of a new drug submission or abbreviated new drug submission or a supplement to either submission, the manufacturer shall establish and maintain records, in a manner that enables an audit to be made, respecting...

(h) any unusual failure in efficacy of that new drug.

C.08.008.
No manufacturer shall sell a new drug unless the manufacturer has, with respect to all the manufacturer's previous sales of that new drug, furnished to the Minister...
(c) within 15 days after the receipt by the manufacturer of information referred to in paragraphs C.08.007(g) and (h), a report on the information received.

### 1.5.2 *Natural Health Products Regulations*

*1.5.2.1 Reaction Reporting (Section 24)*

Section 24.

24.(1) A licensee shall provide the Minister with
(a) a case report for each serious adverse reaction to the natural health product that occurs inside Canada, within 15 days after the day on which the licensee becomes aware of the reaction; and
(b) a case report for each serious unexpected adverse reaction to the natural health product that occurs inside or outside Canada, within 15 days after the day on which the licensee becomes aware of the reaction.

(2) A licensee who sells a natural health product shall annually prepare and maintain a summary report that contains a concise and critical analysis of
(a) all adverse reactions to the natural health product that have occurred inside Canada; and
(b) all reactions for which a case report is required to be provided under subsection (1), that have occurred
(i) during the previous 12 months, and
(ii) at a dose used or tested for the diagnosis, treatment or prevention of a disease or for modifying organic functions in humans.

(3) If after reviewing a case report provided under subsection (1) or after reviewing any other safety data relating to the natural health product, the Minister has reasonable grounds to believe that the natural health product may no longer be safe when used under the recommended conditions of use, the Minister may request that, within 30 days after the day on which the request is received, the licensee
(a) provide to the Minister a copy of any summary report prepared under subsection (2); or
(b) prepare and provide to the Minister an interim summary report containing a concise and critical analysis of
(i) all adverse reactions to the natural health product that have occurred inside Canada, and

(ii) all reactions for which a case report is required to be provided under subsection (1), that have occurred

(A) since the date of the most recent summary report prepared under subsection (2), and

(B) at a dose used or tested for the diagnosis, treatment or prevention of a disease or for modifying organic functions in humans.

# 2 GENERAL PROCEDURES FOR EXPEDITED ADVERSE REACTION REPORTING

Every MAH should put into place written procedures for the receipt, evaluation, and reporting of ARs.

ARs for the marketed health products covered by this Guidance document are to be reported to the MHPD. The preferred reporting format for AR reporting by MAHs is as follows:

- the Council for International Organizations of Medical Sciences (CIOMS) I form (http://www.cioms.ch).

Health Canada also provides a voluntary reporting form by which consumers and health professionals can report ARs:

- Report of Suspected Adverse Reaction due to Health Products Marketed in Canada (Vaccines Excluded) HC/SC 4016 form (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/form/ar-ei_form_e.html).

The CIOMS I form is still, however, Health Canada's preferred format for MAHs to report ARs.

## 2.1 Domestic and Foreign Adverse Reaction Reports

To facilitate the processing of AR reports, the MAH should indicate if the report is domestic or foreign by clearly noting the country where the reaction occurred on the reporting form.

The regulatory reporting time clock is considered to start on the day when any personnel of the MAH first has all of the information that satisfies the minimum criteria for an AR report (see Section 3.1). This date should be considered day 0.

### 2.1.1 Domestic Adverse Reaction Reports

AR reports concerning reactions occurring in Canada to a product that is marketed in Canada are considered "domestic" AR reports.

In order to report in accordance with the Regulations[1, 2, 3], it is sufficient that each MAH report to the MHPD in an expedited fashion (within 15 calendar days of receiving the relevant information) the following domestic reports:

- **serious** ARs
- **unusual failure in efficacy** reports for new drugs.

### 2.1.2 Foreign Adverse Reaction Reports

AR reports concerning reactions occurring outside Canada to a product in which at least one active ingredient is marketed in Canada are considered "foreign" reports.

In order to report in accordance with the Regulations[1, 2, 3], it is sufficient that each MAH report to the MHPD in an expedited fashion (within 15 calendar days of receiving the relevant information) the following foreign reports:

- **serious unexpected** ARs.

The time frame dates from the time that the MAH first learns of a serious unexpected AR. However, MAHs are expected to seek ways to accelerate communications between themselves and their affiliates.

All foreign serious unexpected AR reports involving foreign products with at least one active ingredient that is also marketed in Canada must be reported to the MHPD in accordance with the Regulations[1, 2, 3], irrespective of variations in the formulation, dosage form, strength, route of administration, or indication.

#### 2.1.2.1 Canadian Access to Medicines Program

In response to public health problems afflicting many developing and least-developed countries, Canada has implemented Bill C-9, *An Act to amend the Patent Act and the Food and Drugs Act* (*The Jean Chrétien Pledge to Africa*). The Act, which received Royal Assent on May 14, 2004, sets out the legislative framework which will allow manufacturers to obtain an authorization (i.e., compulsory licence) allowing them to make, construct and use a patented invention solely for the purpose of exporting a pharmaceutical product to eligible importing countries, provided that manufacturers meet certain conditions. Regulations supporting this Act are available in the *Canada Gazette* Part II, Vol. 139, No. 11, issued Wednesday June 1, 2005.

For ARs to health products sold under the Canadian Access to Medicines Program to Developing and least Developed countries, MAHs, when faxing or mailing AR reports to Health Canada, are requested to specify the following on their letter or fax cover page: FOREIGN ADVERSE REACTION, CANADIAN ACCESS TO MEDICINES PROGRAM.

## 2.2 Serious Adverse Reaction Reports

A serious adverse reaction is defined in the Regulations[4, 5] as a noxious and unintended response to a drug or natural health product that occurs at any dose and that requires in-patient

hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death.

Medical and scientific judgement by a qualified health care professional should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition from the Regulations[4, 5]. Health Canada asks that these cases be reported on an expedited basis as well.

## 2.3 Unexpected Adverse Reaction Reports

An AR is considered unexpected when its nature (i.e., specificity or outcome), severity or frequency is not consistent with the term or description used in the product labelling. In cases where the MAH is uncertain whether an AR is expected or unexpected, the AR should be treated as unexpected.

For both domestic and foreign reports, expectedness is determined from relevant Canadian labelling such as the product monograph, labelling standards, information approved for market authorization, or the product label.

For cases that involve a fatal outcome, AR reports should be considered unexpected unless the product labelling specifically states that the AR may be associated with a fatal outcome.

"Class ARs" should not automatically be considered to be expected for the subject health product. "Class ARs" should be considered expected only if described as specifically occurring with the product in the product labelling as illustrated in the following examples:

- "As with other health products of this class, the following undesirable effect occurs with Product X."
- "Health products of this class, including Product X, can cause..."

If the AR has not been documented with Product X, statements such as the following are likely to appear in the product labelling:

- "Other health products of this class are reported to cause..."
- "Health products of this class are reported to cause..., but no reports have been received to date with Product X."

In these situations, the AR should not be considered as expected for Product X.

## 2.4 Other Adverse Reaction Report Types

### 2.4.1 Unusual Failure in Efficacy

For the purpose of this Guidance document, any unusual failure in efficacy of a drug covered by Part C, Division 8 of the *Food and Drug Regulations*[2] shall be treated as a reportable AR. Any unusual failure in efficacy **concerning only New Drugs marketed in Canada** must be reported to the MHPD, within 15 calendar days of the receipt of information by the MAH.

The underlying principle is that if a health product fails to produce the expected pharmacological or therapeutic benefit, there may be an adverse outcome for the patient, including an exacerbation of the condition for which the medication is being taken. Since no health product can be expected to be effective in 100% of the patients, clinical judgement should be exercised by a qualified health care professional to determine if the problem reported is related to the product itself, rather than one of treatment selection or disease progression. One example of unusual failure in efficacy is a previously well-stabilized condition that deteriorates when the patient changes to a different brand or receives a new prescription. In cases where the MAH is uncertain whether an AR should be considered as a report of unusual failure in efficacy, the AR should be treated as a case of unusual failure in efficacy and submitted to Health Canada accordingly.

### 2.4.2 Overdose

Reports of overdose with no associated adverse outcomes should not be reported as ARs. Cases of overdose associated with serious ARs are considered subject to expedited reporting. They should be routinely followed up to ensure that the information is as complete as possible with regard to symptoms, treatment, and outcome. The MAH should collect any available information on overdose related to its products.

### 2.4.3 Pregnancy Exposure

MAHs are expected to follow up all pregnancy reports from health care professionals or consumers where the embryo/foetus could have been exposed to one of its health products. The MAH must apply all principles outlined in this Guidance document and the Regulations[1, 2, 3] pertaining to reporting requirements, including determination of seriousness and minimal criteria for submitting an AR report. When an active substance, or one of its metabolites, has a long half-life, this should be taken into account when considering whether a foetus could have been exposed (e.g., if health products taken before the gestational period should be considered).

### 2.4.4 Discontinued Products

In accordance with the Regulations[1, 2, 3], the MAH must report any AR information received prior to the discontinuation of sale in Canada but is not obliged to report information received following the product's discontinuation unless otherwise required by Health Canada. However, it is important to note that in the event a MAH discontinues sale of a product, if the AR was known to them before the discontinuation of sale, they must still report all ARs as per the expedited reporting requirements even if the end of the 15-day reporting timeframe as required by the Regulations[1, 2, 3] is after the date on which sales were discontinued.

When expired and unexpired lots of a discontinued product are available in pharmacies, the MAH is still under obligation to report ARs to the MHPD when required by Health Canada. Even though it is conceivable that the MAH only becomes aware of ARs after the discontinuation and after all lots have expired, they must still report these reactions to Health Canada on request.

# 3 GOOD CASE MANAGEMENT PRACTICES

## 3.1 Minimum Criteria for an Adverse Reaction Report

Complete information for the final description and evaluation of an AR report may not be available within the time frame required for reporting. Nevertheless, for regulatory purposes, AR reports must be submitted within the prescribed time, as long as the following minimum criteria are met:

(a) An identifiable reporter (source)
(b) An identifiable patient
(c) A suspect product
(d) An adverse reaction

Ideally, more comprehensive information would be available on all cases from the outset, but in practice MAHs will often have to follow up after initially submitting the report to seek additional information. Follow-up AR reports should be clearly labelled as such. The MAH is expected to exercise due diligence to collect any key data elements (see Section 3.8) that are lacking at the time of initially submitting the report.

It is important that at the time of the original report, sufficient details about the patient and reporter be collected and retained to enable future investigations, within the constraints imposed by applicable data privacy laws.

## 3.2 Assessing Patient and Reporter Identifiability

Patient and reporter identifiability is important to avoid case duplication, and facilitate follow-up of appropriate cases. The term "identifiable" in this context refers to the verification of the existence of a patient and a reporter. Provided that the existence of a patient and a reporter can be confirmed, AR cases without specific identifiers are considered reportable. All parties submitting case information or approached for case information should be identifiable: not only the initial reporter (the initial contact for the case), but also others supplying information.

One or more of the following should automatically qualify a patient as identifiable: age (or age category, e.g., adolescent, adult, elderly), gender, or patient identification number. In addition, in the event of second-hand reports, every reasonable effort should be made to verify the existence of an identifiable patient and reporter.

In the absence of qualifying descriptors, a report referring to a definite number of patients should not be regarded as a case until the minimum four criteria for case reporting are met. For example, "Two patients experienced..." or "a few patients experienced" should be followed up for patient-identifiable information before reporting to the MHPD.

## 3.3 The Role of Narratives

The objective of the narrative is to summarize all relevant clinical and related information, including patient characteristics, therapy dates, medical history, clinical course of the event(s), diagnosis, and AR(s) including the outcome, laboratory evidence (including normal ranges), and any other information that supports or refutes an AR. The narrative should serve as a comprehensive, stand-alone "medical story". The information should be presented in a logical time sequence; ideally this should be presented in the chronology of the patient's experience, rather than in the chronology in which the information was received. In follow-up reports, new information should be clearly identified.

Abbreviations and acronyms should be avoided, with the possible exception of laboratory parameters and units. Key information from supplementary records should be included in the report, and their availability should be mentioned in the narrative and supplied on request. Any relevant autopsy or post-mortem findings should be summarized in the narrative and related documents should be provided according to applicable regulation and if allowed by applicable data privacy laws. Personal information should only be submitted within the constraints imposed by Canadian privacy laws.

Information (e.g., ARs, indication, and medical conditions) in the narrative should be accurately reflected in appropriate data fields of the reporting form.

## 3.4 Follow-up Information

Follow-up information should be actively sought and submitted as it becomes available for appropriate amendment to the database and files in the MHPD. Follow-up AR reports should be clearly labelled as such. In the follow-up report, specific reference should be made to the initial report by including the date the initial report was submitted to MHPD and the MAH number specific to the report.

When additional medically relevant information is received for a previously reported case, the reporting time clock is considered to begin again for submission of the follow-up report. In addition, a case initially classified as a non-expedited report, would qualify for expedited reporting upon receipt of follow-up information that indicates the case should be re-classified (e.g., from non-serious to serious).

In any scheme to optimize the value of follow-up, the first consideration should be prioritization of case reports by importance. The priority for follow-up should be as follows: cases which are (1) serious and unexpected, (2) serious and expected, and (3) non-serious and unexpected. Although non-serious and unexpected cases are not expedited, MAHs are encouraged to pursue follow-up information on these reports. In addition, cases of "special interest" also deserve extra

attention as high priority (e.g., ARs under enhanced or active surveillance at the request of Health Canada), as well as any cases that might lead to a labelling change decision.

Follow-up information should be obtained, via a telephone call and/or site visit and/or a written request. The MAH should ask specific questions it would like to have answered. Follow-up methods should be tailored towards optimizing the collection of missing information. Written confirmation of details given verbally should be obtained whenever possible. All attempts to obtain follow-up information (whether or not successful) should be documented as part of the case file, particularly on the priority cases. The number of follow-up attempts along with the date and time of each is recommended to reflect sufficient diligence.

To facilitate the capture of clinically relevant and complete information, use of a targeted questionnaire/specific form is encouraged, preferably at the time of the initial report. Ideally, qualified health care professionals should be involved in the collection and the direct follow-up of reported cases. For serious ARs, it is important to continue follow-up and report new information until the outcome has been established or the condition is stabilized. The amount of time devoted to follow up such cases is a matter of the qualified health care professional's judgement.

Follow-up information should be updated in the narrative sequentially by date. Corresponding data fields should be updated on the reporting form.

## 3.5 Evaluation and Coding of Adverse Reaction Reports

The purpose of careful medical review by qualified health care professionals is to ensure correct interpretation of medical information. Preferably, information about the case should be collected from the healthcare professionals who are directly involved in the patient's care. Regardless of the source of an AR report, the MAH should carefully review the report for the quality and completeness of the medical information. The review should include, but is not limited to, the following considerations:

- Is a diagnosis possible?
- Have the relevant diagnostic procedures been performed?
- Were alternative causes of the reaction(s) considered?
- What additional information is needed?

The Medical Dictionary for Regulatory Activities (MedDRA), an ICH initiative (ICH M1), is an internationally accepted, clinically validated medical terminology developed to share regulatory information about medical products used by humans. MedDRA provides a set of terms which consistently categorizes medical information and is meant to standardize the terminology through which medical regulatory information is classified, stored, retrieved, presented and

communicated. In order to avoid loss or distortion of communicated information, it is recommended that MedDRA be used as a standard for the coding of AR reports.

Every effort should be made to use AR terms consistently and in accordance with recommended standards for diagnosis. The report should include the verbatim term as used by the reporter, or an accurate translation of it. Any MAH personnel receiving reports should provide an unbiased and unfiltered report of the information from the reporter. While the report recipient is encouraged to actively query the reporter to elicit the most complete account possible, inferences and imputations should be avoided in report submission. However, clearly identified evaluations by the MAH are considered appropriate.

When a case is reported by a consumer, his/her description of the event should be retained, although confirmatory or additional information from any relevant qualified health care professionals should also be sought and included.

## 3.6 Contractual Agreements

The marketing of many health products increasingly takes place through contractual agreements between two or more companies, which may market the same product in the same or different countries or regions. Arrangements vary considerably with respect to inter-MAH communication and regulatory responsibilities, therefore it is very important that explicit licensing or contractual agreements specify the processes by which an exchange of safety information, including timelines and regulatory reporting responsibilities, are taking place. Safety personnel should be involved in development of any agreements from the beginning. Processes should be in place to avoid duplicate reporting to the regulatory authority (e.g., assigning the responsibility to one MAH for literature screening).

Whatever the nature of the arrangement, the MAH is ultimately responsible for regulatory reporting. Therefore, every effort must be made between the contracting partners to minimize the data exchange period so as to promote compliance with MAH reporting responsibilities.

## 3.7 Records to be Held for Auditing (C.01.017)

The *Food and Drug Regulations*[13] require that records of the reports and AR case reports be maintained to permit audit or submission on request. A minimum 25 year retention period is recommended. It is also recommended that these records be easily accessible within 72 hours.

Information regarding the Post-Market Reporting Compliance inspection programme conducted by the Health Products and Food Branch Inspectorate is available through the following documents: *Inspection Strategy for Post-Market Surveillance* (POL-0041), and *Risk Classification of Post-Market Reporting Compliance Observations* (GUI-0063).

## 3.8 Key Data Elements

The following is a list of suggested items that enhance the quality of an AR report. Attempts should be made to obtain information on as many listed items as are pertinent to the case.

**1. Patient Details**

- Other relevant identifier (patient number, for example)
- Gender
- Age, age category (e.g., adolescent, adult, elderly)
- Height and weight
- Pre-existing conditions
- Medical history
- Relevant family history

**2. Suspected Health Product(s)**

- Brand name as reported
- Common Name (e.g., INN)
- For natural health products, it is important to include the Latin binomial, author reference, family, type of extract (e.g., aqueous versus alcoholic, including percent of solvent), part of the plant used (in the case of a herbal product), ingredients and quantity of each (for combination products - the suspected ingredient), and potency (for homeopathic products)
- Batch/lot number
- Indication(s) for which suspect health product was prescribed or tested
- Dosage form and strength
- Daily dose (specify units, e.g., mg, ml, mg/kg) and regimen
- Route of administration
- Starting date and time
- Stopping date and time, and duration of treatment

**3. Other Treatment(s)**

The same information as in item 2 should be provided for the following:

- Concomitant health products (including non-prescription, over-the-counter medicinal products, natural health products, dietary supplements, complementary and alternative therapies, etc.)
- Relevant medical devices

**4. Details (all available) of AR(s)**

- Full description of reaction(s), including body site and severity
- The criterion (or criteria) for regarding the report as serious if reported as such
- Description of the reported signs and symptoms
- Specific diagnosis for the reaction
- Onset date (and time) of reaction

- Stop date (and time) or duration of reaction
- Dechallenge and rechallenge information
- Relevant diagnostic test results and laboratory data
- Setting (e.g., hospital, out-patient clinic, home, nursing home)
- Outcome (recovery and any sequelae)
- For a fatal outcome, stated cause of death
- Relevant autopsy or post-mortem findings
- Relatedness of product to reaction(s)/event(s)

**5. Details on Reporter of an AR**

- Name
- Mailing address
- Electronic mail address
- Telephone and/or facsimile number
- Reporter type (consumer, healthcare professional, etc.)
- Profession (specialty)

**6. Administrative and MAH Details**

- Source of report (spontaneous, epidemiological study, patient survey, literature, etc.)
- Date the event report was first received by MAH
- Country in which the reaction occurred
- Type (initial or follow-up) and sequence (first, second, etc.) of case information reported to Health Canada
- Name and address of MAH
- Name, address, electronic mail address, telephone number, and facsimile number of contact person of MAH
- MAH's identification number for the case (the same number should be used for the initial and follow-up reports on the same case).

# 4 AR REPORTS BY SOURCE

## 4.1 Unsolicited Reports

### 4.1.1 Spontaneous Reports

A spontaneous report is defined by the ICH[10] as an unsolicited communication by a health care professional or consumer to a MAH, regulatory authority (i.e., Health Canada) or other organization that describes one or more ARs in a patient who was given one or more health products and that is not derived from a study or any organized data collection scheme.

#### 4.1.1.1 Consumer Reports

Consumer AR reports should be handled as spontaneous reports irrespective of any subsequent "medical confirmation". Emphasis should be placed on the quality of the report and not on its source.

If a MAH receives a report from a consumer, it is recommended that the MAH encourage the patient to report the reaction through his or her physician or pharmacist. Failing this approach, the MAH should attempt to obtain as much information as possible from the patient. If the minimum reporting criteria are met and the report is considered relevant by a qualified health care professional, the case is considered "reportable" and must be forwarded to the MHPD within 15 calendar days (if serious). Even if reports received from consumers do not qualify for regulatory reporting, the cases should be retained.

#### 4.1.1.2 Reports to the Canadian Adverse Reaction Monitoring Regional Offices

If a MAH becomes aware of a report that has been submitted by a practitioner or consumer to one of the official Canadian Adverse Reaction Monitoring Regional Offices (listed on the reverse of Health Canada's AR reporting form, HC/SC 4016), the MAH must also submit the report to the MHPD and should clearly indicate that the report was also sent to a Canadian Adverse Reaction Monitoring Regional Office. To obtain information on reports submitted to the Canadian Adverse Reaction Monitoring Regional Office or the National Centre, the MAH may visit the Health Canada web site for access to the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) AR database or contact the MHPSEIB directly (see Appendix 4 for contact information).

### 4.1.2 Scientific Literature Reports

Every MAH is expected to screen the worldwide scientific literature on a regular basis by accessing widely used systematic literature reviews or reference databases. The frequency of the literature searches should be at least every two weeks. Cases of ARs from the scientific and medical literature, including relevant published abstracts from meetings and draft manuscripts, might qualify for expedited reporting. A regulatory reporting form with relevant medical information must be provided for each identifiable patient. The publication reference(s) should be given as the report source; additionally a copy of the article should accompany the report. All MAH offices are encouraged to be aware of publications in their local journals and to bring them to the attention of the MAH safety department as appropriate.

The regulatory reporting time clock starts as soon as the MAH has knowledge that the case meets minimum criteria for reportability.

If the product source, brand, or trade name is not specified, the MAH should assume that it was its product, although the report should indicate that the specific brand was not identified.

If multiple products are mentioned in the article, a report should be submitted only by the MAH whose product is suspected. The suspect product is that identified as such by the article's author.

### 4.1.3 Stimulated Reporting

Stimulated reports are those that may have been motivated, prompted or induced and can occur in certain situations, such as notification by a Health Care Professional Communication (HCPC), public advisory, literature report, publication in the press, or questioning of health care professionals by MAH representatives. These reports should be considered unsolicited in nature and must be reported to the MHPD in accordance with the Regulations[1, 2, 3].

### 4.1.4 Active Surveillance

Active surveillance seeks to ascertain all adverse events via a continuous pre-organized process, including safety-related patient registries. A registry as defined by the CIOMS, is an organized collection of data on humans within a particular disease group or other special group (e.g., cancer, pregnancy, birth-defect, organ transplant, and serious skin disease registries). Reports of adverse events that occur in the context of a safety-related patient registry, or other patient safety-related initiative should be considered unsolicited in nature and must be reported to the MHPD in accordance with the Regulations[1, 2, 3] if

they meet the minimum criteria for reportability. Reports from registries established by the MAH for reasons other than monitoring patient safety with respect to a specific issue should be handled as solicited reports (see Section 4.2).

### 4.1.5 Reports via the Internet

MAHs should regularly screen websites under their management or responsibility for potential AR case reports. MAHs are not expected to screen external websites for AR information. However, if a MAH becomes aware of an AR on a website that it does not manage, the MAH should review the case and determine whether it should be reported.

MAHs should consider utilising their websites to facilitate AR data collection, e.g., by providing AR forms for reporting or by providing appropriate contact details for direct communication.

Cases from the Internet should be handled as unsolicited reports. For the determination of reportability, the same minimum criteria (e.g., identifiable reporter, identifiable patient, suspect product and AR) should be applied as for cases provided via other ways.

### 4.1.6 Other Unsolicited Reports

If a MAH becomes aware of a case report from non-medical sources (e.g., the lay press or other media), it should be handled as an unsolicited report. For the determination of reportability, the same minimum criteria (e.g., identifiable reporter, identifiable patient, suspect product and AR) should apply as for other reports.

## 4.2 Solicited Reports

Post-marketing regulations generally refer to two types of safety reports: those that are reported spontaneously (spontaneous reports) and those that are reported as part of the conduct and analysis of a clinical or non-clinical study involving a health product (i.e., study reports). There is, however, an increase in types of reports that do not fall neatly into either of these categories. Many of these newer reports are generated by marketing programs used by pharmaceutical companies and through the increasing use of methods to encourage contact between consumers and the pharmaceutical company. These are clearly not generated in the usual spontaneous manner that is the premise upon which spontaneous reporting systems are based; they are usually obtained incidentally to the main purpose of the program. For this reason, such reports are regarded as solicited in nature and one cannot infer implied causality, the convention for spontaneous reports.

Solicited reports are defined by the ICH[10] as those derived from organized data collection systems, which include clinical trials, registries (see Section 4.1.4), post-approval named patient

use programs, other patient support and disease management programs, surveys of patients or health care providers, or information gathering on efficacy or patient compliance. Solicited reports do not originate with any safety issue or safety study, but invariably arise in the course of interaction with patients for unrelated purposes. AR reports obtained from any of these sources should not be considered unsolicited. Solicited reports should also not be confused with stimulated reports (see Section 4.1.3).

For the purposes of AR reporting, solicited reports should only be submitted if there is a reasonable possibility that the health product caused the AR. A "reasonable possibility" means that the relationship cannot be ruled out. For example, using the World Health Organization criteria for causality applicable to AR reporting, any case reports that fall within the criteria of Certain, Probable, Possible, or Unlikely (see Appendix 6) must be reported to Health Canada. In any case where an underlying illness or another health product may have contributed to the adverse event, the report should still be considered an AR, as the causality cannot be ruled out.

### 4.2.1 Studies

#### 4.2.1.1 Market Authorization Holder Sponsored Studies

Studies conducted on **marketed health products that are not subject to** Part C, Division 5 of the *Food and Drug Regulations* or Part 4 of the *Natural Health Products Regulations* (e.g., phase IV studies) should be monitored in a way that ensures that all serious domestic ARs and serious unexpected foreign ARs are reported to the MAH by the investigator(s) so that the MAH can provide such reports to the MHPD within the 15-day period specified in the Regulations[1, 2, 3].

Investigators should be provided with the definition of what constitutes a serious AR for reporting purposes. In such cases, it is important to try to distinguish between "reactions" and "events", not only for administrative purposes but also to minimize the instances of reporting health outcomes (events) that are clearly unrelated to therapy. MAHs should help investigators understand their role in assessing the possible relationship between an adverse event and the administration of a health product during post-marketing studies.

Studies conducted on marketed health products used in clinical trials that **are subject to** Part C, Division 5 of the *Food and Drug Regulations* or Part 4 of the *Natural Health Products Regulations* have separate reporting requirements, as detailed in the Regulations and are not within the scope of this Guidance document. See Appendix 5 for contact information.

#### 4.2.1.2 Non-Market Authorization Holder Sponsored Studies

A MAH may receive study AR reports where their product was a comparator treatment (and therefore used in accordance with approved labelling) or was a product the patient was taking concomitant to the study medication but was suspected of causing an AR. The source of these reports may be another MAH who is sponsoring the study, a private investigator or an academic centre. The MAH must apply all principles outlined in this Guidance document and the Regulations[1, 2, 3] pertaining to reporting requirements, including determination of seriousness, causality, and minimal criteria for submitting an AR report. The MAH should not alter the causality assessment of the trial product(s) provided by the trial sponsor and should include any narrative of the trial sponsor regarding causality, if available. The MAH should assess causality on its own marketed health product(s).

#### 4.2.1.3 Post-Study Events

Although such information is not routinely sought or collected by the sponsor, serious adverse events that occurred after the patient had completed a clinical study (including any protocol-required post-treatment follow-up) will possibly be reported by an investigator to the sponsor. Such cases should be regarded for expedited reporting purposes as though they were study reports. Therefore, a causality assessment and determination of expectedness are needed for a decision on whether or not expedited reporting is required.

### 4.2.2 Blinded Study Reports (in Phase IV)

If the MAH receives a report from the investigator that is blinded to individual patient treatment, the code must be broken before submitting the report to the MHPD. Although it is advantageous to retain the blind for all patients prior to final study analysis, it is recommended that, when a serious AR occurs, the MAH seek a third party to break the blind only for that specific patient, even if the investigator has not broken the blind. It is also recommended that, when possible and appropriate, the blind be maintained for individuals such as biometrics personnel, who are responsible for analysis and interpretation of results at the conclusion of the study.

## 4.3 Regulatory Authority Sources

Individual serious unexpected AR reports originating from foreign regulatory authorities are subject to expedited reporting to Health Canada by each MAH. Re-submission of serious AR cases obtained from MHPSEIB without any new information to MHPSEIB is not usually necessary.

To avoid duplicate reporting, reports received by the MAH from the MHPD (e.g., AR reports, case reports published in the Canadian Adverse Reaction Newsletter (CARN), CADRMP AR database) should not be re-submitted to Health Canada by the MAH as they are already contained within the CADRMP AR database. The MAH may, however, wish to inform Health Canada of their assigned identification number for reference, but the case need not be re-submitted.

It is recommended that the MAH consult the CADRMP AR database or request line-listing summaries to obtain reports that were sent directly to the MHPD. Requests for line-listing summaries from the CADRMP AR database should be made in writing (letter, fax or e-mail) to MHPD. Copies of AR reports must be requested through the Access to Information and Privacy Division of Health Canada and will require payment of the applicable fee.

# 5 SUMMARY REPORTS

In order to report in accordance with the Regulations[1, 3], the MAH must, on an annual basis and when requested by the Director under the Regulations[1, 3], prepare a summary report. Summary reports prepared by MAHs should be Periodic Safety Update Reports (PSURs) in accordance with the standards defined in the ICH E2C(R1)[9] guideline.

PSURs based on multiples of six months with the summary bridging report are acceptable. Further information regarding the summary bridging report integrating the information presented in two or more PSURs to cover a specified period is available in the ICH E2C(R1)[9] guideline. The summary report is to be maintained by the MAH on site or be easily accessible and, when requested, it is to be submitted to the MHPD within 30 calendar days.

MAHs should consult the ICH E2C(R1)[9] guideline for the format and content for comprehensive periodic safety updates of marketed health products. The summary report in PSUR format as per ICH E2C(R1)[9] should consist of the following sections: Introduction, World-wide Market Authorization Status, Update of Regulatory Authority or MAH Actions Taken for Safety Reasons, Patient Exposure, Presentation of Individual Case Histories, Studies, Other Information, Overall Safety Evaluation, and Conclusion.

# 6 APPENDICES

## Appendix 1 Glossary: Definitions and Terminology

Adverse Event[10] **(AE)**
An adverse event is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

"**Adverse reaction (AR)**" for the purpose of this Guidance document means a noxious and unintended response to a marketed health product covered by this document and includes "adverse drug reaction" as defined in the *Food and Drug Regulations*[4] and "adverse reaction" as defined in the *Natural Health Products Regulations*[5].

> Adverse Drug Reaction
> Adverse drug reaction as defined in the *Food and Drug Regulations*[4] is 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.
>
> Adverse Reaction
> Adverse reaction as defined in the *Natural Health Products Regulations*[5] is a noxious and unintended response to a natural health product that occurs at any dose used or tested for the diagnosis, treatment or prevention of a disease or for modifying an organic function.

**Brand Name (*Food and Drug Regulations*[4])**
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.

**Brand Name (*Natural Health Products Regulations*[5])**
Means a name in English or French, whether or not it includes the name of a manufacturer, corporation, partnership or individual
(a) that is used to distinguish the natural health product; and
(b) under which a natural health product is sold or advertised.

**Common Name (*Food and Drug Regulations*[4])**
With reference to a drug, the name in English or French by which the drug is
(a) commonly known, and

(b) designated in scientific or technical journals, other than the publications referred to in Schedule B to the Act.

**Common Name**[14] **(Natural Health Products)**
For any medicinal or non-medicinal ingredient contained in a natural health product, the name by which it is commonly known and is designated in a scientific or technical reference.

**Domestic AR**
Adverse reaction occurring in Canada.

**Drug**
According to the *Food and Drugs Act*[6], a drug includes any substance or mixture of substances manufactured, sold or represented for use in:

a. the diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical state, or the symptoms thereof in human beings or animals,

b. restoring, correcting or modifying organic functions in human beings or animals, or

c. disinfection in premises in which food is manufactured, prepared or kept.

**Expected AR**[10]
An AR whose nature (i.e., specificity or outcome), severity or frequency is consistent with the term or description used in the product labelling should be considered expected.

**Expedited AR Report**
The following must be reported by the MAH within 15 calendar days of receiving information:

- any serious domestic AR,
- any serious unexpected foreign AR, and
- any domestic unusual failure in efficacy for a new drug.

**Foreign AR**
Adverse reaction occurring outside Canada.

"**Health product**" for the purpose of this Guidance document includes drugs, medical devices, and natural health products. Drugs include both prescription and nonprescription pharmaceuticals; biotechnology products and biologically-derived products such as vaccines, serums, and blood derived products; cells, tissues and organs; disinfectants; and radiopharmaceuticals. Note however, as set out in Section 1.1, that only some of these health products fall within the scope of the AR reporting covered by this Guidance Document.

"**Market authorization holder (MAH)**" for the purpose of this Guidance document means a "manufacturer" as defined in the *Food and Drug Regulations*[7] or a licensee in the *Natural Health Products Regulations*.

> Manufacturer or Distributor
> The manufacturer or a distributor as defined in the *Food and Drug Regulations*[7] is a person, including an association or partnership, who under their own name, or under a trade-, design or word mark, trade name or other name, word or mark controlled by them, sells a food or drug.

**Natural Health Product (NHP)**
A substance set out in Schedule 1 of the *Natural Health Products Regulations*[5] or a combination of substances in which all the medicinal ingredients are substances set out in Schedule 1 of the *Natural Health Products Regulations*, a homeopathic medicine or a traditional medicine, that is manufactured, sold or represented for use in

- the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms in humans;
- restoring or correcting organic functions in humans; or
- modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health.

However, a natural health product does not include a substance set out in Schedule 2 of the *Natural Health Products Regulations*, any combination of substances that includes a substance set out in Schedule 2 of the *Natural Health Products Regulations* or a homeopathic medicine or a traditional medicine that is or includes a substance set out in Schedule 2 of the *Natural Health Products Regulations*.

**Periodic Safety Update Report**[9] **(PSUR)**
The PSUR is a practical and achievable mechanism for summarizing interval safety data, and for conducting an overall safety evaluation. It is a tool for MAHs to conduct systematic analyses of safety data on a regular basis. In addition to covering ongoing safety issues, the PSUR should also include updates on emerging and/or urgent safety issues, and major signal detection and evaluation that are addressed in other documents.

**Product Monograph**[15] **(PM)**
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.

**Phase IV Study**[16] **(Drugs)**
All studies performed after the drug has been approved by the regulator for the market, and

related to the approved indication. These studies are often important for optimizing the drug's use. They may be of any type but must have valid scientific objectives. Commonly conducted studies include safety studies designed to support use under the approved indication such as mortality and morbidity studies, or epidemiological studies.

**Phase IV Study**[17] **(Natural Health Products)**
All studies performed after the NHP has been approved by the regulator for the market and related to the approved conditions of use. These studies are often important for optimizing the NHP's use. They may be of any type but must have valid scientific objectives. Commonly conducted studies include safety studies and studies designed to support use under the approved conditions of use, such as mortality and morbidity studies or epidemiological studies.

**Qualified Health Care Professional**
A person who is a member in good standing of a professional medical, nursing or pharmacists' association and entitled to provide health care under the laws of the jurisdiction in which the person is located and other individuals retained by the MAH who have the appropriate health care education and therapeutic expertise.

**Registry**[12]
An organized collection of data on humans within a particular disease group or other special group (e.g., cancer, pregnancy, birth-defect, organ transplant, and serious skin disease registries).

"**Serious adverse reaction**" for the purpose of this Guidance Document means a noxious and unintended response to a marketed health product covered by this document that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, that causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death and includes "serious adverse drug reaction" as defined in the *Food and Drug Regulations*[4] and "serious adverse reaction" as defined in the *Natural Health Products Regulations*[5].

> Serious Adverse Drug Reaction
> A serious adverse drug reaction as defined in the *Food and Drug Regulations*[4] is a noxious and unintended response to a drug that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death.
>
> Serious Adverse Reaction
> A serious adverse reaction as defined in the *Natural Health Products Regulations*[5] is a noxious and unintended response to a natural health product that occurs at any dose and that requires in-patient hospitalization or a prolongation of existing hospitalization, that

causes congenital malformation, that results in persistent or significant disability or incapacity, that is life threatening or that results in death.

**Serious Unexpected Adverse Drug Reaction (*Food and Drug Regulations*[4])**
A serious adverse drug reaction that is not identified in nature, severity or frequency in the risk information set out on the label of the drug.

**Serious Unexpected Adverse Reaction (*Natural Health Products Regulations*[5])**
A serious adverse reaction that is not identified in nature, severity or frequency in the risk information set out on the label of the natural health product.

**Solicited Report**[10]
Solicited reports are those derived from organized data collection systems, which include clinical trials, registries, post-approval named patient use programs, other patient support and disease management programs, surveys of patients or health care providers, or information gathering on efficacy or patient compliance. Adverse event reports obtained from any of these should not be considered spontaneous.

**Spontaneous Report**
A spontaneous report is an unsolicited communication by a health care professional or consumer to a company, regulatory authority or other organization (e.g., WHO, Regional Centre, Poison Control Centre) that describes one or more adverse reactions in a patient who was given one or more medicinal products* and that does not derive from a study or any organized data collection scheme.
*As extracted from ICH E2D[10]. For the purposes of this Guidance document, a medicinal product is a health product.

**Stimulated Report**
A report that may have been motivated, prompted or induced and can occur in certain situations, such as notification by a Health Care Professional Communication (HCPC), public advisory, literature report, publication in the press, or questioning of health care professionals by MAH representatives.

**Unexpected AR**[10]
An AR whose nature, severity, specificity, or outcome is not consistent with the term or description used in the local/regional product labelling (e.g., Package Insert or Summary of Product Characteristics) should be considered unexpected. When a MAH is uncertain whether an AR is expected or unexpected, the AR should be treated as unexpected.

An expected AR with a fatal outcome should be considered unexpected unless the approved Canadian product labelling specifically states that the AR might be associated with a fatal outcome.

## Appendix 2 Endnotes, References

### References

[1]*Food and Drug Regulations*, Part C, Division 1, Adverse Reaction Reporting (C.01.016), C.R.C., c. 870.

[2]*Food and Drug Regulations*, Part C, Division 8, New Drugs (C.08.007, C.08.008), C.R.C., c. 870.

[3]*Natural Health Products Regulations*, Section 24, Reaction Reporting, C.R.C., SOR/2003-196.

[4]*Food and Drug Regulations*, Part C, Division 1, General (C.01.001), C.R.C., c. 870.

[5]*Natural Health Products Regulations*, Interpretation, C.R.C., SOR/2003-196.

[6]*Food and Drugs Act*, Revised Statues of Canada, Interpretation, 1985, c. F-27, as amended.

[7]*Food and Drug Regulations*, Part A, Interpretation (A.01.010), C.R.C., c. 870.

[8]International Conference on Harmonisation, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2A) (1994).

[9] International Conference on Harmonisation, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (ICH E2C(R1)) (2005).

[10]International Conference on Harmonisation, Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2D) (2003).

[11]International Conference on Harmonisation, Pharmacovigilance Planning (ICH E2E) (2004).

[12]Council for International Organizations of Medical Sciences, Current Challenges in Pharmacovigilance: Pragmatic Approaches, Report of CIOMS Working Group V (Geneva, Switzerland: CIOMS, 2001), 72.

[13]*Food and Drug Regulations*, Part C, Division 1, Adverse Reaction Reporting (C.01.017), C.R.C., c. 870.

[14]Health Canada, Adverse Reaction Reporting (Natural Health Products) (2004).

[15]Health Canada, Guidance for Industry: Product Monograph (2004).

[16]Health Canada, Guidance for Clinical Trial Sponsors: Clinical Trial Applications (2003).

[17]Health Canada, Clinical Trials for Natural Health Products (NHPs) (2005).

## Appendix 3 Abbreviations

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|---|---|
| AE | Adverse Event |
| AR | Adverse Reaction |
| ATI | Access to Information |
| BGTD | Biologics and Genetic Therapies Directorate |
| CADRMP | Canadian Adverse Drug Reaction Monitoring Program |
| CIOMS | Council for International Organizations of Medical Sciences |
| CTA | Clinical Trial Application |
| HC | Health Canada |
| HPFB | Health Products and Food Branch |
| ICH | International Conference on Harmonisation |
| INN | International Nonproprietary Name |
| MAH | Market Authorization Holder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHPD | Marketed Health Products Directorate |
| MHPSEIB | Marketed Health Products Safety and Effectiveness Information Bureau |
| NHP | Natural Health Product |
| NHPD | Natural Health Products Directorate |
| PSUR | Periodic Safety Update Report |
| TPD | Therapeutic Products Directorate |
| The Regulations | Collectively, the *Food and Drug Regulations* and the *Natural Health Products Regulations* |
| WHO | World Health Organization |

## Appendix 4 Contact Information

The preferred method of reporting ARs is by fax or mail. All AR reports and summary reports/PSURs for marketed health products covered by this Guidance document should be sent to:

Canadian Adverse Drug Reaction Monitoring Program
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Tunney's Pasture
Address Locator: 0701C
Ottawa, Ontario
K1A 0K9
Telephone: (613) 957-0337
Facsimile: (613) 957-0335

Access to Information

For requests for line-listing summaries, consult the Access to Information website at:
http://www.tbs-sct.gc.ca/gos-sog/atip-aiprp/index_e.asp

CIOMS publications may be obtained directly from:

Council for International Organizations of Medical Sciences
c/o World Health Organization
avenue Appia
CH-1211 Geneva 27
Switzerland
Telephone: +41 (22) 791 21 11
Facsimile: +41 (22) 791 07 46
Web: www.cioms.ch

International Conference on Harmonisation guidance documents may be obtained from:

ICH Secretariat
c/o IFPMA
30 rue de St-Jean
P.O. Box 758
1211 Geneva 13
Switzerland
Telephone: +41 (22) 338 32 06
Facsimile: +41 (22) 338 32 30
Web: www.ich.org

## Appendix 5 Other Adverse Reaction Reporting Programs

Health Canada monitors health and safety risks related to the sale and use of chemicals, drugs and vaccines, food, pesticides, medical devices and certain consumer products. ARs concerning products that are not within the scope of this Guidance document may be reported to Health Canada and its partners. Please refer to the following web site and table for further information: http://www.hc-sc.gc.ca/ahc-asc/media/reaction/index_e.html.

| **Products** | **Program** |
|---|---|
| Clinical Trial Pharmaceutical Drugs | Therapeutic Products Directorate<br>Health Products and Food Branch |
| Clinical Trial Biologics, Radiopharmaceuticals, Blood and Blood Components | Biologics and Genetic Therapies Directorate<br>Health Products and Food Branch |
| Clinical Trial Natural Health Products | Natural Health Products Directorate<br>Health Products and Food Branch |
| Consumer Products | Consumer Product Safety Bureau<br>Healthy Environments and Consumer Safety Branch |
| Cosmetics | Cosmetics Program<br>Healthy Environments and Consumer Safety Branch |
| Drugs and Natural Health Products used in Animals | Veterinary Drugs Directorate<br>Health Products and Food Branch |
| Food | Office of Food Safety and Recall<br>Canadian Food Inspection Agency |
| Medical Devices | Health Products and Food Branch Inspectorate<br>Health Products and Food Branch |
| Pesticides | Pest Management Regulatory Agency |
| Radiation-Emitting Devices | Consumer and Clinical Radiation Protection Bureau (CCRPB)<br>Healthy Environments and Consumer Safety Branch |
| Vaccines in Humans | Canadian Adverse Events Following Immunization Surveillance System (CAEFISS)<br>Public Health Agency of Canada |
| Veterinary Biologics | Veterinary Biologics Section<br>Canadian Food Inspection Agency |

## Appendix 6 World Health Organization Causality Algorithm

Causality Assessment of Suspected Adverse Reactions developed by the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden

| TERM | DESCRIPTION | COMMENTS |
|---|---|---|
| Certain | A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary. | It is recognized that this stringent definition will lead to very few reports meeting the criteria, but this is useful because of the special value of such reports. It is considered that time relationships between drug administration and the onset and course of the adverse event are important in causality analysis. So also is the consideration of confounding features, but due weight must placed on the known pharmacological and other characteristics of the drug product being considered. Sometimes the clinical phenomena described will also be sufficiently specific to allow a confident causality assessment in the absence of confounding features and with appropriate time relationships, e.g. penicillin anaphylaxis. |
| Probable / Likely | A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition. | This definition has less stringent wording than for "certain" and does not necessitate prior knowledge of drug characteristics or clinical adverse reaction phenomena. As stated no rechallenge information is needed, but confounding drug administration underlying disease must be absent. |
| Possible | A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear. | This is the definition to be used when drug causality is one of other possible causes for the described clinical event. |
| Unlikely | A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations. | This definition is intended to be used when the exclusion of drug causality of a clinical event seems most plausible. |

| | | |
|---|---|---|
| Conditional / Unclassified | A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination. | |
| Unassessable / Unclassifiable | A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified. | |

## Appendix 7 Summary of Expedited Reporting Requirements

| TYPE OF REACTIONS | REPORT WITHIN 15 CALENDAR DAYS | TYPE OF HEALTH PRODUCT (NEW OR ALL) |
|---|---|---|
| **DOMESTIC REPORTS** | | |
| Serious Unexpected | YES | ALL |
| Serious Expected | YES | ALL |
| Non-Serious Unexpected | NO | ALL |
| Unusual Failure in Efficacy | YES | NEW |
| **FOREIGN REPORTS** | | |
| Serious Unexpected | YES | ALL |
| Serious Expected | NO | ALL |
| Non-Serious Unexpected | NO | ALL |
| Unusual Failure in Efficacy | NO | NEW |