

Guidance Document for Industry - Reporting Adverse Reactions to Marketed Health Products*

(Effective Date: 2011-03-02)

*Canada Vigilance Adverse Reaction Monitoring
Program and Database, a program of MedEffect™
Canada*

**Marketed health products covered by this guidance document are listed in Section 1.1 Scope and exclude blood, blood components, cells, tissues and organs, medical devices, and veterinary drugs.*



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Canada

Health Canada is the federal department responsible for helping the people of Canada maintain and improve their health. We assess the safety of drugs and many consumer products, help improve the safety of food, and provide information to Canadians to help them make healthy decisions. We provide health services to First Nations people and to Inuit communities. We work with the provinces to ensure our health care system serves the needs of Canadians.

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The *Guidance Document for Industry – Reporting Adverse Reactions to Marketed Health Products* is available on the Internet at the following address:

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Foreword

Guidance documents are meant to provide assistance 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 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 document, 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 relevant sections of other applicable guidance documents.

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1 Introduction

1.1 Scope

This guidance document provides Market Authorization Holders (MAHs) with assistance on how to comply with the *Food and Drugs Act*, the *Food and Drug Regulations*, and the *Natural Health Products Regulations* with respect to reporting adverse reactions (ARs) to marketed health products. ARs for marketed health products within the scope of this guidance document are to be reported to the Canada Vigilance Adverse Reaction Monitoring Program of the Marketed Health Products Directorate (MHPD) of Health Canada. This guidance document covers the collection of AR reports by the MHPD for the following marketed health products:

- 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, vaccines and fractionated blood products), but excluding blood and blood components;
- 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*.

In addition to the requirement for MAHs to submit AR reports 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}.

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*⁴ and Part 4 of the *Natural Health Products Regulations*, respectively, are not within the scope of this guidance document.

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*¹ and “adverse reaction” as defined in the *Natural Health Products Regulations*⁵.

“Adverse drug reaction” as defined in the *Food and Drug Regulations*¹ 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*¹ 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*¹ 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 products regulated under the *Food and Drugs Regulations* ("drugs") and the *Natural Health Products Regulations* ("natural health products"). Drugs include both prescription and non-prescription pharmaceuticals; biotechnology products and biologically-derived products such as vaccines, serums, and blood derived products; 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 or abnormal physical state, or its symptoms, 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:

- a. the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms in humans;
- b. restoring or correcting organic functions in humans; or
- c. 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 the entity that holds the Notice of Compliance, the Drug Identification Number (DIN), the Natural Product Number (NPN), the Homeopathic Medicine Number (DIN-HM), or the product licence.

“**Qualified health care professional**” for the purpose of this guidance document means a person who is a member in good standing of a professional medical, nursing, pharmacists’ or other health care practitioner 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.

1.3 Adverse Reaction Reporting by Market Authorization Holders

Every MAH is required to report ARs known to them involving their marketed health products in accordance with the requirements of the *Food and Drugs Act* and the *Regulations*^{1,2,3}. The success of Health Canada’s AR reporting system 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 of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance documents: *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*⁷ (ICH E2A), *Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs*⁸ (ICH E2C(R1)), and *Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting*⁹

(ICH E2D), *Pharmacovigilance Planning*¹⁰ (ICH E2E), and the *Report of the Council for International Organizations of Medical Sciences (CIOMS) V Working Group: Current Challenges in Pharmacovigilance: Pragmatic Approaches*¹¹.

1.4 Adverse Reactions

This guidance document applies to adverse reactions rather than adverse events (AEs). ARs to marketed health products covered by this document may be generated from unsolicited and solicited reports.

An AR, in contrast to an AE, is characterized by the fact that a causal relationship between the drug and the occurrence is suspected. The definition of adverse reaction (see Section 1.2) implies that there is a suspected relatedness to the administered health product. Health professionals and consumers report adverse reactions because of their suspicion of the relatedness of an adverse event to a health product. The description of experiences in these reports should therefore be considered adverse reactions. Reportable ARs also include those suspected of being the result of drug interactions (e.g., drug-drug interactions, drug-natural health product interactions, drug-food interactions).

An adverse event, as defined in ICH E2D⁹, 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.

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 Prohibition and Serious Adverse Drug Reaction Reporting (C.01.016, C.01.017)

Prohibition

C.01.016.

No manufacturer shall sell a drug unless the manufacturer complies with the conditions set out in sections C.01.017 to C.01.019.

Serious Adverse Drug Reaction Reporting

C.01.017.

The manufacturer shall submit to the Minister a report of all information relating to the following serious adverse drug reactions within 15 days after receiving or becoming aware of the information, whichever occurs first:

- (a) any serious adverse drug reaction that has occurred in Canada with respect to the drug; and
- (b) any serious unexpected adverse drug reaction that has occurred outside Canada with respect to the drug.

1.5.1.2 Annual Summary Report and Case Reports (C.01.018)

C.01.018.

(1) The manufacturer shall prepare an annual summary report of all information relating to adverse drug reactions and serious adverse drug reactions to the drug that it received or became aware of during the previous 12 months.

(2) The annual summary report shall contain a concise, critical analysis of the adverse drug reactions and serious adverse drug reactions to the drug.

(3) In preparing the annual summary report, the manufacturer shall determine, on the basis of the analysis referred to in subsection (2), whether there has been a significant change in what is known about the risks and benefits of the drug during the period covered by the report and shall include its conclusions in this regard in the summary report.

(4) If, in preparing the annual summary report, the manufacturer concludes that there has been a significant change, it shall notify the Minister without delay, in writing, unless this has already been done.

(5) The Minister may, for the purposes of assessing the safety and effectiveness of the drug, request in writing that the manufacturer submit to the Minister one or both of the following:

- (a) the annual summary reports;
- (b) the case reports relating to the adverse drug reactions and serious adverse drug reactions to the drug that are known to the manufacturer.

(6) The Minister shall, after giving the manufacturer an opportunity to be heard, specify a period for the submission of the annual summary reports or case reports, or both, that is reasonable in the circumstances, and the manufacturer shall submit the reports within that period.

1.5.1.3 Issue-related Summary Report (C.01.019)

C.01.019.

(1) The Minister may, for the purposes of assessing the safety and effectiveness of the drug, request in writing that the manufacturer submit to the Minister an issue-related summary report.

(2) The report shall contain a concise, critical analysis of the adverse drug reactions and serious adverse drug reactions to the drug, as well as case reports of all or specified adverse drug reactions and serious adverse drug reactions to the drug that are known to the manufacturer in respect of the issue that the Minister directs the manufacturer to analyze in the report.

(3) The Minister shall, after giving the manufacturer an opportunity to be heard, specify a period for the submission of the report that is reasonable in the circumstances. The Minister may specify a period that is shorter than 30 days if the Minister needs the information in the report to determine whether the drug poses a serious and imminent risk to human health.

(4) The manufacturer shall submit the report within the specified period.

1.5.1.4 Maintenance of Records (C.01.020)

C.01.020.

(1) The manufacturer shall maintain records of the reports and case reports referred to in sections C.01.017 to C.01.019.

(2) The manufacturer shall retain the records for 25 years after the day on which they were created.

1.5.1.5 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*

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 to 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:

- for drugs, the Council for International Organizations of Medical Sciences (CIOMS) I form (http://www.cioms.ch/form/frame_form.htm);
- for natural health products, the Mandatory Adverse Reaction Reporting Form for Industry (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/ar-ei_indus_form-eng.php). The Mandatory Adverse Reaction Reporting Form for Industry has been developed as an alternate reporting format to accommodate AR reporting for other product types such as natural health products and human cells, tissues and organs.

2.1 Domestic and Foreign Adverse Reaction Reports

For drugs, MAHs must submit domestic and foreign AR reports to the MHPD pursuant to Part C, Division 1 (C.01.016, C.01.017) and for new drugs must submit reports of unusual failure in efficacy pursuant to Part C, Division 8 (C.08.007, C.08.008) of the *Food and Drug Regulations* once their drugs are sold on the market in Canada. These reporting obligations (see sections 2.1.1 and 2.1.2) for MAHs commence when the MAH sells a drug, which can occur for example when a MAH offers a drug for sale, exposes a drug for sale or has a drug in its possession for sale and distribution.

For natural health products, MAHs must submit domestic and foreign AR reports to the MHPD as set out in Section 24 of the *Natural Health Products Regulations* once their health product is licensed to be marketed in Canada.

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. In addition, box 24a of the CIOMS I form or box A4 of the Mandatory Adverse Reaction Reporting Form for Industry should reflect the entity (e.g., the MAH) who is reporting the AR to Health Canada. The official document is the reporting form and not the cover letter.

The regulatory reporting time clock is considered to start on the day when the MAH (the entity that holds the DIN, NPN, or DIN-HM (see Section 1.2)) 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. MAHs are expected to seek ways to accelerate communications between themselves and their affiliates to promote compliance with MAH adverse reaction reporting responsibilities.

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 that 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.**

All foreign serious unexpected AR reports involving the MAH’s foreign products with the same combination of active ingredients irrespective of variations in the formulation, dosage form, strength, route of administration, or indication, that is also marketed in Canada must be reported to the MHPD in accordance with the Regulations^{1, 2, 3}

(e.g., a MAH that sells a marketed health product in Canada with active ingredients X, Y, and Z, must report all foreign serious unexpected AR reports involving their foreign products with active ingredients X, Y, Z).

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

2.1.2.1 Canada's Access to Medicines Regime

In response to public health problems afflicting many developing and least-developed countries, Canada passed on May 14, 2004 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 came into force on May 14, 2005, creates a legislative framework that enables 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. The provisions of the Act are now incorporated in the *Patent Act* and the *Food and Drugs Act*, following their amendment after the coming into force of the Act.

Compulsory licence holders are subject to the requirements for reporting foreign adverse reactions to health products sold under Canada's Access to Medicines Regime (CAMR). Compulsory licence holders submitting these reports to the MHPD are requested to specify the following on the cover sheet: FOREIGN ADVERSE REACTION, CANADA'S ACCESS TO MEDICINES REGIME.

2.2 Serious Adverse Reaction Reports

A serious adverse reaction is defined in the Regulations^{1, 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^{1, 5}. Health Canada asks that these cases be reported on an expedited basis as well. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

2.3 Unexpected Adverse Reaction Reports

An AR is considered unexpected when its nature (i.e., specificity or outcome), severity or frequency is either not identified, or 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 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

The MAH may use the CIOMS I form to report an unusual failure in efficacy of a new drug in accordance with Part C, Division 8 of the *Food and Drug Regulations*². For **New Drugs marketed in Canada**, domestic reports of unusual failure in efficacy must be reported to the MHPD within 15 calendar days of the receipt of information by the MAH. Inquiries regarding new drug status for health products marketed in Canada should be referred to the appropriate Directorate (i.e., Biologics and Genetic Therapies Directorate or Therapeutic Products Directorate).

The underlying principle is that if a health product fails to produce the expected intended effect, there may be an adverse outcome for the patient, including an exacerbation of the condition for which the health product is being used. Clinical judgement should be exercised by a qualified health care professional from the MAH to determine if the problem reported is related to the product itself, rather than one of treatment selection or disease progression since health products cannot be expected to be effective in 100% of the patients. 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. Another example of a case that should be reported on an expedited basis is a life-threatening infection where the failure in efficacy seems to be due to the development of a newly resistant strain of bacterium previously regarded as susceptible.

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 such and submitted to the MHPD accordingly. For consumer reports, emphasis should be placed on the quality of the report and not on its source.

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 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 and consumers where the embryo/foetus could have been exposed to one of its health products. For consumer reports, it is appropriate to seek permission to only follow-up with the health care professional. 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. Although the MAH is not obliged to report any new cases of adverse reactions received following the product's discontinuation, Health Canada may request the provision of this information. If a serious AR was known to the MAH before the discontinuation of sale, they must still report 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. Follow-up information for cases known to the MAH prior to the discontinuation of sale should be reported to the MHPD in accordance with the Regulations, and should be sought as part of the follow-up practices described under Section 3.4.

When expired and unexpired lots of a discontinued product are available in pharmacies, the MAH is under obligation to report ARs to the MHPD if this information was received by the MAH prior to the discontinuance. Health Canada may also request the MAH to provide information that it receives following the discontinuation of sales.

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 follow-up in accordance with the collection, use and disclosure provisions of the *Personal Information Protection and Electronic Documents Act* or equivalent provincial privacy legislation.

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. AR cases without specific identifiers meet the first two reporting criteria outlined in section 3.1. However, follow-up information should be actively sought and submitted as it becomes available. 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. 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.

One or more of the following should automatically qualify a patient as identifiable: age or age category (e.g., adolescent, adult, elderly), gender, patient identification number, or reference to “a patient”. In the absence of qualifying descriptors (e.g., age, gender), a report referring to a 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. The minimum criteria must be met for each reported patient.

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 (e.g., rechallenge information). The narrative should serve as a comprehensive, stand-alone “medical story”.

Abbreviations and acronyms should be avoided, with the possible exception of laboratory parameters and units. Key information from supplementary records including summarized relevant autopsy or post-mortem findings should be included in the report, and their availability should be mentioned in the narrative and supplied on request. Clinical judgement should be exercised by a qualified health care professional from the MAH to determine what information should be submitted. Personal identifiers should only be submitted in accordance with the collection, use and disclosure provisions of the *Personal Information Protection and Electronic Documents Act* or equivalent provincial privacy legislation.

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. Specific reference should be made to the initial report by including the MAH number specific to the report either in the follow-up report or on the fax cover sheet.

Follow-up information should be clearly identified, and should be updated in the narrative sequentially by the date it was received by the MAH. Corresponding data fields should be updated on the reporting form.

When additional medically relevant information is received for a previously reported case, the reporting time clock (see Section 2.1) is considered to begin again for submission of the follow-up report. Follow-up information received by the MAH for serious domestic ARs and serious unexpected foreign ARs must be reported to the MHPD within 15 calendar days. 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. If appropriate, written confirmation of details given verbally should be obtained. 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.

3.5 Evaluation and Coding of Adverse Reaction Reports

The purpose of careful medical review by qualified health professionals is to ensure correct interpretation of medical information. Preferably, information about the case should be collected from the health 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:

- Has a diagnosis been assigned?
- 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 as part of the follow-up practices described under Section 3.4.

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 the 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.01.020)

The *Food and Drug Regulations*¹ require that records of the annual summary reports and AR case reports be maintained. For drugs, the MAH must retain records for 25 years after the day on which they were created. It is also recommended that these records be easily accessible within 72 hours.

For natural health products, records of the annual summary reports and AR case reports should be maintained to permit audit or submission on request. A minimum 25 year retention period is recommended from the date the record was created. It is also recommended that these records be easily accessible within 72 hours.

Information regarding the Post-Market Reporting Compliance inspection program 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**
 - Unique identifier (to readily locate the case for follow-up purposes; do not use the patient's name or initials)
 - 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 [the brand name is the name assigned by the MAH, used to distinguish the health product, and under which the health product is sold or advertised, and includes any name

- extensions or modifiers (prefix or suffix)]
 - Common Name (e.g., INN)
 - For natural health products, it is important to include the Latin binomial, author reference, family (genus and species), 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 homeopathic products, potency of each ingredient). If a particular ingredient in a combination is suspected, this should also be identified.
 - 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
 - For vaccines, indicate the number of previous doses of each vaccine. For example, if the event occurred after a series of several vaccinations (e.g., 3 doses of hepatitis B vaccine) give details of prior immunizations in the narrative
- 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**
- Reporter type (consumer, health professional, etc.)
 - Profession (specialty)
- 6. Administrative and MAH Details**
- Source of report (e.g., clinical trial, literature, spontaneous, regulatory authority)
 - 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. Adverse Reaction Reports by Source

4.1 Unsolicited Reports

An unsolicited report is a spontaneous report which is defined by the ICH11 as an unsolicited communication by a health 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 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 health professional or permission should be sought to contact the consumer’s health professional. In addition, the MAH should attempt to obtain as much information as possible from the patient. Consumers report adverse reactions because of their suspicion of the relatedness of an adverse event to a health product. The description of the experiences in these reports should therefore be considered adverse reactions.

If the minimum reporting criteria are met and the report is considered relevant by a qualified health professional from the MAH, the case is considered “reportable” and must be forwarded to the MHPD in accordance with the Regulations^{1,2,3}. Even if reports received from consumers do not qualify for regulatory reporting, the cases should be retained.

4.1.2 Reports to the Canada Vigilance Regional Offices

If a MAH becomes aware of a report that has been submitted by a practitioner or consumer to one of the official Canada Vigilance Regional Offices, the MAH must also submit the report to the MHPD in accordance with the Regulations^{1,2,3} and should clearly indicate that the report was also sent to a Canada Vigilance Regional Office. Please note that MAHs should submit reports to the MHPD Canada Vigilance Program, coordinates listed in Appendix 4, and not the Canada Vigilance Regional Offices.

4.1.3 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. It is recommended that the frequency of the literature searches be at least every two weeks. A qualified health care professional from the MAH should use their clinical judgement to determine the appropriate frequency of literature searches based on the health product marketed by the MAH. Cases of ARs from the scientific and medical literature, including relevant published abstracts from meetings and draft manuscripts, might qualify for expedited reporting. A 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, the MAH is expected to submit the article, and is expected to translate the abstract into either English or French if the article is not published in one of the official languages. 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.

For foreign literature reports, all foreign serious unexpected ARs involving the MAH’s foreign products with the same combination of active ingredients irrespective of variations in the formulation, dosage form, strength, route of administration, or indication, that is also marketed in Canada must be reported to the MHPD in accordance with the Regulations^{1,2,3} (see Section 2.1.2).

If the product source, brand, or trade name is not specified, the MAH should assume that it was its own 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(s) is/are those identified as such by the article's author.

4.1.4 Stimulated Reports

Stimulated reports are those that may have been motivated, prompted or induced and can occur in certain situations, such as notification by a Health Professional Communication (HPC), Health Canada-issued Public Advisory and/or Public Communication (PC), 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}.

4.1.5 Reports via the Internet

MAHs should regularly screen Web sites 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 (i.e., identifiable reporter, identifiable patient, suspect product and AR) should be applied as for cases provided via other ways. If the minimum reporting criteria are met and the report is considered relevant by a qualified health care professional from the MAH, the case is considered "reportable" and must be forwarded to the MHPD in accordance with the Regulations^{1, 2, 3}.

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 (i.e., identifiable reporter, identifiable patient, suspect product and AR) should apply as for other reports.

4.2 Solicited Reports

Solicited reports are defined by the ICH⁹ as 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. 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. Such reports are regarded as solicited in nature and one cannot infer implied causality, the convention for spontaneous reports. Solicited reports should also not be confused with stimulated reports (see Section 4.1.4).

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 as determined by a qualified health care professional of the MAH. 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 the MHPD. 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 Patient Support and Disease Management Programs

A number of solicited reports are generated through the increasing use of methods to encourage contact between consumers and the pharmaceutical company, such as through marketing programs as part of another patient support and disease management program used by pharmaceutical companies. Examples of these programs include, but are not limited to, telephone services for patients to obtain direct advice, nurse-initiated calls for medicine compliance management, surveys collecting other patient data, and establishment of large patient registries. These reports are clearly not generated in the usual spontaneous manner that is the premise upon which unsolicited reporting systems are based; they are usually obtained incidentally to the main purpose of the program. Reports generated through these programs are considered reportable in accordance with the Regulations^{1, 2, 3}.

4.2.2 Reports from Studies

For studies, this section of the guidance document refers to the post-market AR reporting requirements for marketed health products, Division 1 (C.01.016 and C.01.017) and Division 8 (C.08.007(h) and C.08.008(c)) of the Food and Drug Regulations and Section 24 of the Natural Health Products Regulations.

MAHs are also subject to AR reporting for health products used in studies where the MAH is the sponsor of the study, in accordance with the requirements listed in Part C, Division 5 of the Food and Drug Regulations⁴, or Part 4 of the Natural Health Products Regulations. These requirements are not within the scope of this guidance document (see Appendix 5 for contact information).

4.2.2.1 Market Authorization Holder Sponsored Studies

Studies subject to post-market AR reporting requirements (e.g., phase IV studies) should be monitored in a way that ensures that all serious domestic ARs, serious unexpected foreign ARs and reports of domestic unusual failure in efficacy for new drugs 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 adverse 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.

Comparator and concomitant products used in these studies are within the scope of this guidance document. It is the sponsor’s responsibility to decide whether active comparator and concomitant product adverse reactions should be reported to the other MAH and/or directly to MHPD. Sponsors should report such events to either the MAH of the active control or to the MHPD.

4.2.2.2 Non-Market Authorization Holder Sponsored Studies

A MAH may receive study AR reports where its 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).

4.2.2.3 Post-Study Adverse Reactions

Although such information is not routinely sought or collected by the sponsor, serious adverse reactions

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 is needed for a decision on whether or not expedited reporting is required.

4.2.3 Blinded Study Reports (in Phase IV)

If the MAH receives a serious domestic AR report or a serious unexpected foreign AR 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. If the product source, brand, or trade name is not specified, the MAH should assume that it was its own product, although the report should indicate that the specific brand was not identified.

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), Canada Vigilance Adverse Reaction Online Database) are not required to be re-submitted to the MHPD by the MAH as they are already contained within the Canada Vigilance Adverse Reaction Database. The MAH may, however, wish to inform the MHPD of their assigned identification number for reference. If the MAH is re-submitting the case with their identification number, the MAH should clearly indicate that the source of the report is Health Canada and should include the Health Canada report ID number in the narrative.

It is recommended that the MAH consult the Canada Vigilance Adverse Reaction Online Database or request line-listing summaries to obtain reports that were sent directly to the Canada Vigilance Regional or National Offices (see Appendix 4 for contact information). Requests for line-listing summaries from the Canada Vigilance Adverse Reaction 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 accordance with the *Food and Drug Regulations*¹, the MAH must, on an annual basis and whenever requested by the Minister, conduct a concise, critical analysis of the adverse drug reactions (ADRs) and serious adverse drug reactions to a drug and prepare a summary report in respect of the reports received during the previous twelve months. In accordance with the *Natural Health Products Regulations*³, the MAH must, on an annual basis, prepare and maintain a summary report that contains a concise and critical analysis of all domestic ARs to a natural health product, and all foreign serious unexpected ARs to a natural health product taken at the recommended dose reported during the previous twelve months.

The selected 12-month period for the annual summary report is specified by the MAH. 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. When Health Canada requests the annual summary report, it is preferred that it be submitted in the Periodic Safety Update Report (PSUR) format in accordance with the standards defined in the ICH E2C(R1)⁸ guideline.

5.1 Summary Reports for Drugs

In accordance with the *Food and Drug Regulations*¹, in preparing the annual summary report, the MAH must determine whether there has been a significant change in what is known about the risks and benefits of the drug. If the MAH concludes from the annual summary report that there has been a significant change, the MAH must inform MHPD in writing, without delay. Examples may include a significant change in the frequency or severity of a known risk or the identification of a previously unknown risk.

5.2 Summary Reports for Natural Health Products

In addition to complying with regulatory requirements to report safety and efficacy information, Health Canada expects that MAHs inform MHPD if the MAH concludes from the annual summary report that there is a significant change in what the MAH knows about the risks and benefits of the natural health product. Examples may include a significant change in the frequency or severity of a known risk or the identification of a previously unknown risk.

5.3 Summary Report Format

The preferred format for annual summary reports prepared by MAHs is the PSUR format. PSURs based on multiples of six months with the summary bridging report are also appropriate. 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)⁸ guideline.

MAHs may also use an annual summary report format as described below. This annual summary report format does not contain information regarding the worldwide market authorization status and completed and planned studies, both of which are included in the PSUR format.

It is acceptable for the MAH to prepare a PSUR in ICH format according to the international PSUR schedule, be it every six months (with a summary bridging report), every year, three years, four years or five years while preparing an annual summary report for the years not covered by the PSUR.

The information included in the annual summary report will vary depending on the adverse reaction cases reported to the MAH and lack of significant new information should be mentioned for each section.

Health Canada expects that the annual summary report will contain the following:

- Introduction
- Changes to the MAH's product safety information
- Significant regulatory actions bearing on safety (domestic and foreign)
- Line listing(s) and summary tabulations (see Section 5.2)
- Critical Analysis:
 - A change in characteristics of expected reactions, e.g., severity, outcome, target population

- Serious unexpected reactions, placing into perspective the cumulative reports since marketing
- Non-serious unexpected reactions
- An increased reporting frequency of expected reactions, including comments on whether it is believed the data reflect a meaningful change in AR occurrence
- Comparative analysis of reporting rates using patient exposure estimate (analyses may be done in the context of amount of sales of the drug or by estimating the number of patient days of exposure)
- The report should also explicitly address any new safety issue on the following (lack of significant new information should be mentioned for each):
 - drug interactions
 - experience with overdose, deliberate or accidental, and its treatment
 - drug abuse or misuse
 - positive or negative experiences during pregnancy or lactation
 - experience in special patient groups (e.g., children, elderly, organ impaired)
 - effects of long-term treatment
- Other information (e.g., information related to effectiveness and late-breaking information)
- Conclusion.

5.4 Line Listing(s) and Summary Tabulations

Health Canada expects that the following types of cases will be included in the line-listing and that attempts will be made to avoid duplicate reporting of cases from the literature and regulatory sources:

- for drugs, from unsolicited sources (see Section 4.1):
 - all domestic and foreign serious ARs
 - all domestic and foreign non-serious unexpected ARs
 - domestic cases of unusual failure in efficacy for new drugs
- for drugs, from solicited sources where there is a reasonable possibility that the drug caused the adverse reaction (see Section 4.2):
 - all domestic and foreign serious ARs
 - domestic cases of unusual failure in efficacy for new drugs
- for drugs, from regulatory authority sources (see Section 4.3):
 - all domestic and foreign serious ARs
 - domestic cases of unusual failure in efficacy for new drugs
- for natural health products, from unsolicited sources and regulatory authority sources, and from solicited sources where there is a reasonable possibility that the natural health product caused the adverse reaction (see Section 4.2):
 - all domestic ARs to a natural health product
 - all serious unexpected foreign ARs to a natural health product taken at the recommended dose.

5.4.1 Presentation of the Line Listing

The line listing(s) should include each patient only once regardless of how many adverse reaction terms are reported for the case. If there is more than one reaction, they should all be mentioned but the case should be listed under the most serious AR as judged by the MAH. It is possible that the same patient may experience different ARs on different occasions (e.g., weeks apart during a study). Such experiences would be treated as separate reports. Under such circumstances, the same patient might then be included in a line-listing more than once, and the line-listings should be cross-referenced when possible. Cases should be organized (tabulated) by body system (standard organ system classification scheme).

The following headings should usually be included in the line listing:

- MAH case reference number
- Country in which the case occurred
- Source of report (e.g., clinical trial, literature, spontaneous, regulatory authority)

- Age and gender
- Daily dose of suspected health product (and, when relevant, dosage form or route)
- Date of onset of the reaction
- Dates of treatment
- Description of reaction (MedDRA terminology is recommended)
- Patient outcome (at case level) (e.g., resolved, fatal, improved, sequelae, unknown). This field does not refer to the criteria used to define a “serious” AR. It should indicate the consequences of the reaction(s) for the patient, using the worst of the different outcomes for multiple reactions.
- Comments, if relevant (e.g., causality assessment if the MAH disagrees with the reporter; concomitant health products suspected to play a role in the reactions directly or by interaction; indication treated with suspect health product(s); dechallenge/rechallenge results if available).

Depending on the health product or circumstances, it may be useful or practical to have more than one line listing, such as for different dosage forms or indications, if such differentiation facilitates presentation and interpretation of the data.

5.4.2 Summary Tabulations

An aggregate summary for each of the line listings should be presented. These tabulations ordinarily contain more terms than patients. It is useful to have separate tabulations (or columns) for serious reactions and for non-serious reactions, for expected and unexpected reactions; other breakdowns might also be appropriate (e.g., by source of report). When the number of cases is very small, or the information inadequate for any of the tabulations, a narrative description, rather than a formal table, is considered suitable.

5.5 Issue-Related Summary Reports for Drugs

Pursuant to the *Food and Drug Regulations*¹, for the purposes of assessing the safety and effectiveness of a drug, the Minister may request in writing that the MAH submit an issue-related summary report. An issue-related summary report must contain a concise, critical analysis of the adverse drug reactions and serious adverse drug reactions to the drug and case reports of all or specified adverse drug reactions and serious adverse drug reactions to the drug that are known to the MAH in respect of the issue that the Minister directs the MAH to analyze in the report.

The adequacy of the content of an issue-related summary report would normally be determined by taking account of what the manufacturer can reasonably provide in the time frame set by the Minister. This would, as a minimum, typically include: an analysis of the risk of the product based on available data and conclusions regarding the safety of the product as marketed in Canada.

Appendix 1 Glossary Definitions and Terminology

Adverse Event⁹ (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*¹ 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*¹ 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*¹)

With reference to a drug, the name, whether or not including the name of any manufacturer, corporation, partnership or individual, in English or French:

- that is assigned to the drug by its manufacturer;
- under which the drug is sold or advertised; and
- 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:

- that is used to distinguish the natural health product; and
- under which a natural health product is sold or advertised.

Canada Vigilance Adverse Reaction Monitoring Program

Health Canada’s Canada Vigilance Adverse Reaction Monitoring Program is responsible for the collection and assessment of adverse reaction reports related to the following marketed health products: pharmaceuticals, biologics (including fractionated blood products and vaccines), natural health products, radiopharmaceuticals and cells, tissues and organs. Canada Vigilance is a program of MedEffectTM Canada and is operated by the Marketed Health Products Directorate.

Common Name (*Food and Drug Regulations*¹)

With reference to a drug, the name in English or French by which the drug is:

- commonly known; and
- designated in scientific or technical journals, other than the publications referred to in Schedule B to the Act.

Common Name (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 or abnormal physical state, or its symptoms, 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

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

An adverse reaction occurring outside Canada to a product with the same combination of active ingredients that is marketed in Canada irrespective of variations in the formulation, dosage form, strength, route of administration, or indication.

Health Product for the purpose of this guidance document includes products regulated under the *Food and Drugs Regulations* (“drugs”) and the *Natural Health Products Regulations* (“natural health products”). Drugs include both prescription and non-prescription pharmaceuticals; biotechnology products and biologically-derived products such as vaccines, serums, and blood derived products; 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 the entity that holds the Notice of Compliance, the Drug Identification Number (DIN), the Natural Product Number (NPN), the Homeopathic Medicine Number (DIN-HM), or the product licence.

MedEffect™ Canada

MedEffect™ Canada has been developed by Health Canada's Marketed Health Products Directorate:

- to provide centralized access to relevant and reliable health product safety information as it becomes available, in an easy to find, easy to remember location. This includes access to Health Canada's advisories, warnings and recalls; the Canadian Adverse Reaction Newsletter (CARN); and the Canada Vigilance Adverse Reaction Online Database;
- to make it as simple and efficient as possible for health professionals and consumers to complete and file adverse reaction reports via Web, phone, fax or mail; and
- to build awareness about the importance of reporting adverse reactions to Health Canada, and how this information is used to identify and communicate potential risks.

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

- a. the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms in humans;
- b. restoring or correcting organic functions in humans; or
- c. 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 Report⁸ (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 Monograph¹² (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 Study¹³ (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 Study¹⁴ (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, pharmacists' or other health care practitioner 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.

Registry¹¹

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).

Sell⁶

Includes offer for sale, expose for sale, have in possession for sale and distribute, whether or not the distribution is made for consideration.

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*¹ 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*¹ 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*¹⁾)

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 Report⁹

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 E2D⁹. 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 Professional Communication (HPC), Health Canada-issued Public Advisory and/or Public Communication (PC), literature report, publication in the press, or questioning of health care professionals by MAH representatives. These reports should be considered unsolicited in nature.

Unsolicited Report

See Spontaneous Report.

Appendix 2 References

- ¹ *Food and Drug Regulations*, Part C, Division 1, C.R.C., c. 870
- ² *Food and Drug Regulations*, Part C, Division 8, 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 5, C. R. C., c.870
- ⁵ *Natural Health Products Regulations*, Interpretation, C.R.C., SOR/2003-196
- ⁶ *Food and Drugs Act*, Revised Statutes of Canada, Interpretation, 1985, c. F-27, as amended
- ⁷ International Conference on Harmonisation, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2A) (1994)
- ⁸ International Conference on Harmonisation, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (ICH E2C(R1)) (2005)
- ⁹ International Conference on Harmonisation, Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2D) (2003)
- ¹⁰ International Conference on Harmonisation, Pharmacovigilance Planning (ICH E2E) (2004)
- ¹¹ Council for International Organizations of Medical Sciences, Current Challenges in Pharmacovigilance: Pragmatic Approaches, Report of CIOMS Working Group V (Geneva, Switzerland: CIOMS, 2001), 72
- ¹² Health Canada, Guidance for Industry: Product Monograph (2004)
- ¹³ Health Canada, Guidance for Clinical Trial Sponsors: Clinical Trial Applications (2003)
- ¹⁴ Health Canada, Clinical Trials for Natural Health Products (NHPs) (2005)

Appendix 3 Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AR	Adverse Reaction
ATI	Access to Information
BGTD	Biologics and Genetic Therapies Directorate
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 of Technical Requirements for Registration of Pharmaceuticals for Human Use
INN	International Nonproprietary Name
MAH	Market Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MHPD	Marketed Health Products Directorate
NHP	Natural Health Product
NHPD	Natural Health Products Directorate
PSUR	Periodic Safety Update Report
TPD	Therapeutic Products Directorate
The Regulations	Collectively, the <i>Food and Drug Regulations</i> and the <i>Natural Health Products Regulations</i>
WHO	World Health Organization

Appendix 4 Contact Information

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

Canada Vigilance Program
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Postal Locator: 0701E
Ottawa, Ontario
K1A 0K9

Telephone: (613) 957-0337
Facsimile: (613) 957-0335
E-mail: CanadaVigilance@hc-sc.gc.ca (DO NOT SEND REPORTS VIA E-MAIL)

For drugs, all summary reports/PSURs should be sent to:

Submission and Information Policy Division (SIPD)
Therapeutic Products Directorate
Health Canada
101 Tunney's Pasture Driveway
Postal Locator: 0201A1
Ottawa, Ontario
K1A 1B9

For natural health products, all summary reports/PSURs should be sent to:

Marketed Biologicals, Biotechnology and Natural Health Products Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Postal Locator: 0701A
Ottawa, Ontario
K1A 0K9

Access to Information

For copies of AR reports, consult the Access to Information Web site 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 34 13
Facsimile: +41 (22) 791 42 86
Web: www.cioms.ch

International Conference on Harmonisation guidance documents may be obtained from:

ICH Secretariat
c/o IFPMA
15, chemin Louis-Dunant
P.O. Box 195
1211 Geneva 20
Switzerland
Telephone: +41 (22) 338 32 06
Facsimile: +41 (22) 338 32 30
Web: www.ich.org

Appendix 5 Adverse Reaction Reporting Programs

Health Canada and its partners collect adverse reaction reports in order to monitor health and safety risks related to the sale and use of a variety of products. In order to avoid delays in reporting, it is important to direct adverse reaction reports to the appropriate program area of expertise. Refer to the Web site and table below, which provide further information on adverse reaction reporting specific to other products that are not within the scope of this guidance document. All adverse reaction reports related to marketed health products should be sent to the Canada Vigilance national office (see Appendix 4 of this guidance document).

Adverse Reaction Reporting for Specific Products:

<http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/reaction-eng.php>

Table 1: Adverse Reaction Reporting Programs

Products	Program Leads
Blood and Blood Components	Biologics and Genetic Therapies Directorate of the Health Products and Food Branch
Clinical Trial Biologics and Radiopharmaceuticals	Biologics and Genetic Therapies Directorate of the Health Products and Food Branch
Clinical Trial Natural Health Products	Natural Health Products Directorate of the Health Products and Food Branch
Clinical Trial Pharmaceutical Drugs	Therapeutic Products Directorate of the Health Products and Food Branch
Consumer Products	Consumer Product Safety Bureau of the Healthy Environments and Consumer Safety Branch
Cosmetics	Cosmetics Program of the Healthy Environments and Consumer Safety Branch
Food	Office of Food Safety and Recall of the Canadian Food Inspection Agency
Human Cells, Tissues and Organs for Transplantation	Canada Vigilance Adverse Reaction Monitoring Program of the Health Products and Food Branch
Medical Devices	Health Products and Food Branch Inspectorate
Pesticides	Pest Management Regulatory Agency
Radiation-Emitting Devices	Consumer and Clinical Radiation Protection Bureau of the Healthy Environments and Consumer Safety Branch
Special Access Programme Drugs	Special Access Programme – Therapeutic Products Directorate of the Health Products and Food Branch
Veterinary Biologics	Veterinary Biologics Section of the Canadian Food Inspection Agency
Veterinary Drugs	Veterinary Drugs Directorate of the Health Products and Food Branch

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 be 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 Post-Market AR Reporting Requirements to MHPD

Type of Reactions	Drug and Natural Health Product ARs to be Reported to MHPD Within 15 Calendar Days
Domestic Reports Unsolicited: Serious Unexpected Serious Expected Non-Serious Unexpected Non-Serious Expected Solicited (e.g., Studies*) Serious Unexpected Serious Expected Non-Serious Unexpected Non-Serious Expected	YES YES NO NO YES YES NO NO
Foreign Reports Unsolicited: Serious Unexpected Serious Expected Non-Serious Unexpected Non-Serious Expected Solicited (e.g., Studies*) Serious Unexpected Serious Expected Non-Serious Unexpected Non-Serious Expected	YES NO NO NO YES NO NO NO

*Studies not subject to clinical trial applications (CTAs)