

**Our Mandate:**

To manage and deliver a national compliance and enforcement program for blood and donor semen; cells, tissues and organs; drugs (human and veterinary); medical devices and natural health products, collaborating with and across, all regions.

# Health Products and Food Branch Inspectorate

## Good Pharmacovigilance Practices (GVP) Guidelines GUI-0102

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**Disclaimer**

*This document does not constitute part of the Food and Drugs Act (Act) or its associated Regulations and in the event of any inconsistency or conflict between that Act or Regulations and this document, the Act or the Regulations take precedence. This document is an administrative document that is intended to facilitate compliance by the regulated party with the Act, the Regulations and the applicable administrative policies.*

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## 1.0 Introduction

The *Food and Drug Regulations*, more specifically sections C.01.016 to C.01.020, C.08.007 (h) and C.08.008 (c), set forth regulatory requirements for manufacturers, including but not limited to, the reporting of adverse drug reactions (ADR) and the reporting of unusual failures in efficacy of new drugs to Health Canada. As part of Health Canada's mandate to maximize the safety, quality and efficacy of health products, Health Canada implemented on August 1, 2004, an inspection program for Good Pharmacovigilance Practices (GVP) (previously known as Post-Market Reporting Compliance). The GVP inspection program is intended to verify that the manufacturer meets the requirements of sections C.01.016 to C.01.020, C.08.007 (h) and C.08.008 (c) of the *Food and Drug Regulations* pertaining to ADR reporting. Within the context of the GVP inspection program, Market Authorization Holders (MAH) and importers are subject to GVP inspections as their name appears on the label and as such may receive ADRs.

The content of this document should not be regarded as the only interpretation of the *Food and Drug Regulations*, nor does it intend to cover every conceivable case. Alternative means of complying with the *Food and Drug Regulations* can be considered with the appropriate justification.

## 2.0 Purpose

The purpose of this guidance document is to provide interpretive guidance to industry on the expectations of inspectors with respect to the adverse drug reaction and post-approval reporting requirements when conducting GVP inspections. These guidelines are designed to facilitate compliance by the regulated industry and to enhance consistency in the application of the regulatory requirements regarding good pharmacovigilance practices.

## 3.0 Scope

The *Food and Drug Regulations* set forth regulatory requirements for manufacturers to report ADRs and to report unusual failure in efficacy of new drugs to Health Canada. Within the context of the GVP inspection program, MAH and importers are subject to GVP inspections as their name appears on the label and as such may receive ADRs.

This guide covers the following drugs marketed in Canada for human use which are subject to GVP inspections:

- pharmaceuticals,
- biologics, including biotechnology products, vaccines and fractionated blood products,
- medical gases, and
- radiopharmaceuticals.

This guide does not currently apply to:

- hard surface disinfectants,
- veterinary products,
- natural health products, and
- whole blood and blood components.

**Table 1.0: Requirements Applicable to the MAH and the Importer**

The responsibilities of the MAH and the importer are outlined below. Based on contractual agreements, the responsibilities may differ as the MAH may contract out any of these responsibilities and the importer may have been delegated more responsibilities than the ones indicated below; however the MAH is required to ensure that all the requirements of the *Food and Drug Regulations* and any relevant Health Canada's guidance documents are met.

	<b>MAH</b>	<b>Importer</b>
<b>Complaints Procedure</b>	X	X
<b>Adverse Drug Reaction (ADR) Procedures</b>	X	X
<b>Receipt of ADR Data</b>	X	X
<b>Evaluation of ADR Data</b>	X	
<b>Reporting of ADR Data to Health Canada</b>	X	
<b>Literature Search</b>	X	
<b>Contractual Agreement</b>	X	X
<b>Validation of Computerized Systems</b>	X	X
<b>Preparation of Annual Summary Report</b>	X	
<b>Preparation of an Issue-related Summary Report</b>	X	
<b>Maintenance of Records</b>	X	X
<b>Receipt of Unusual Failure in Efficacy for New Drugs</b>	X	X
<b>Reporting of Unusual Failure in Efficacy for New Drugs</b>	X	

## 4.0 Regulation

Please note that an interpretation may apply to more than one regulation and in those instances, the interpretation is only stated once.

### 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

#### Regulation

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.

#### Rationale

MAHs and importers are required to collect comprehensive ADR information in a timely manner. This information must be submitted to Health Canada within the prescribed timelines in order for Health Canada to monitor the safety and effectiveness of drugs marketed in Canada. MAHs and importers must have a system in place that enhances the overall quality of the ADR report while ensuring that accurate and complete pharmacovigilance information is provided to Health Canada.

#### Interpretation

**Note:** Importers who have been delegated activities related to pharmacovigilance by the foreign MAH are required to meet all requirements outlined in the section below. Please note that all importers should have available evidence that the below requirements are met.

### Adverse Drug Reaction Reporting

1. Procedures and Processes
  - 1.1 MAH and importers should have in place written procedures describing the handling of all complaints regarding a drug product. The procedure should include but not be limited to the following:
    - 1.1.1 provisions for timely and thorough review to determine whether the complaint represents an ADR;
    - 1.1.2 personnel responsible to receive the incoming correspondence (phone calls, letter, email, etc.) relating to potential ADRs through product complaints;
    - 1.1.3 how a unique identifier is assigned to each case; and
    - 1.1.4 clear and defined processes on ADR/complaint, evaluation and follow-up.

- 1.2 MAHs and importers should have in place systems and procedures for the receipt, handling, evaluation and reporting of ADRs that are adequate to effectively sustain ADR reporting within 15 days of receipt to Health Canada of domestic serious expected and unexpected ADRs, foreign serious unexpected ADRs, as well as any follow-up information for initial case reports.
- 1.3 MAHs should have in place adequate procedures for ADR receipt, handling, evaluation and reporting and should include but not be limited to the following:
  - 1.3.1 Requirement to report to Health Canada within 15 calendar days of receipt by the MAH, reports of serious ADRs occurring within Canada, and serious unexpected ADRs occurring outside of Canada and any unusual failure in efficacy for new drugs occurring within Canada, if applicable;

**Note:** As indicated in Section 2.1 of the Marketed Health Products Directorate (MHPD) document [Guidance Document for Industry - Reporting Adverse Reactions to Marketed Health Products](http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2011-guidance-directrice_reporting-notification/index-eng.php), ([http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/\\_guide/2011-guidance-directrice\\_reporting-notification/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2011-guidance-directrice_reporting-notification/index-eng.php)), the regulatory reporting time clock is considered to start on the day when the MAH first has all of the information that satisfies the minimum criteria for an ADR report. 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 ADR reporting responsibilities.
  - 1.3.2 Address all the specific Canadian regulatory requirements, such as when notification is required, definition of serious and non-serious adverse reactions, definition of unusual failure in efficacy of new drugs, if applicable, retention of all records associated with ADR, etc;
  - 1.3.3 Requirement to have a qualified health care professional to evaluate and assess ADR reports, including the process to review ADRs;
  - 1.3.4 Identifying the 4 minimum criteria (an identifiable reporter (source), an identifiable patient, a suspect product and an adverse reaction) for submitting a case;
  - 1.3.5 Identifying key personnel who are responsible for forwarding the ADR reports to Health Canada;
  - 1.3.6 Procedure on how complaints and ADRs are tracked/logged in;
  - 1.3.7 Procedure on how the MAH is to be notified of foreign serious unexpected drug reactions;
  - 1.3.8 The decision-making process to assess reportability of ADRs;
  - 1.3.9 The responsibilities for the final approval of ADR evaluation and appropriate follow-up;
  - 1.3.10 Reference to the contact information (fax or mail) for the appropriate department within the MHPD where reports are to be submitted;
  - 1.3.11 Requirement to effectively follow-up with case reports, to document all attempts to obtain follow-up information and submit information to the appropriate department within the MHPD as it becomes available;
  - 1.3.12 Requirement to conduct a critical analysis of ADR reports received and preparation of a summary report on an annual basis, or at the request of Health Canada; and
  - 1.3.13 Requirement to effectively maintain records of ADRs for a minimum of 25 years after the day on which they were created.

- 1.4 Importers should have in place adequate procedures for ADRs receipt, handling, evaluation (for determination of complaints or ADR) and forwarding ADRs to the MAH and should include but not be limited to the following:
    - 1.4.1 Procedure on how complaints and ADRs are tracked/logged in ;
    - 1.4.2 Procedure on how complaints are assessed in order to determine if it is an ADR ;
    - 1.4.3 Identifying key personnel who are responsible for forwarding the ADRs reports to the MAH ;
    - 1.4.4 Requirement to report ADRs to the MAH within an appropriate timeframe to allow for expedited reporting (if required) ;
    - 1.4.5 Requirement to follow up with the MAH to ensure that ADRs have been assessed and sent to Health Canada, if required ;
    - 1.4.6 Requirement to maintain records of all ADRs received and ADRs sent to the MAHs and subsequent correspondence; and
    - 1.4.7 Requirement to effectively maintain records of ADRs for a minimum of 25 years after the day on which they were created.
  - 1.5 Procedures should be written, reviewed and approved by qualified personnel.
  - 1.6 Procedures should be made available to all relevant personnel involved in pharmacovigilance activities before the procedures are effective.
  - 1.7 Procedures should be reviewed on a periodic basis to ensure that they accurately reflect current practice.
  - 1.8 Changes to procedures should be tracked and documented.
  - 1.9 Deviations from procedures relating to pharmacovigilance activities should be documented.
  - 1.10 When part or all pharmacovigilance activities are performed by a third party, MAH and importers should review procedures to ensure that procedures are adequate and compliant with applicable requirements stated in the *Food and Drug Regulations*. Copies of the procedures should be readily available to the inspector.
2. Receipt of ADR Data
- 2.1 Market Authorization Holders and Importers
    - 2.1.1 System should be in place to track, log in, and document all correspondence received by the consumer service.
    - 2.1.2 Process should be in place for timely and thorough review of complaints to determine whether they represent an ADR.
    - 2.1.3 All suspected ADRs should be recorded, tracked and logged appropriately.
    - 2.1.4 Mechanisms should be in place to ensure that all ADRs have been appropriately identified and transferred to the relevant department.
    - 2.1.5 An unique identifier should be assigned to each suspected ADR case.

- 2.1.6 Personnel responsible for receiving the incoming correspondence (For example: phone calls, letters, e-mails) relating to potential ADRs through product complaints should be identified in procedures.

### 3. Evaluation of ADR data

#### 3.1 Market Authorization Holders

- 3.1.1 ADR reports should be appropriately coded. The Medical Dictionary for Regulatory Activities (MedDRA) terminology is recommended to code ADR reports.
- 3.1.2 The ADR evaluation, including but not limited to, seriousness and expectedness assessment should be completed in a manner which would ensure expedited reporting timelines are met. For both domestic and foreign reports, the expectedness should be determined from the relevant Canadian labelling such as the product monograph, labelling standards, information approved for market authorization, or the product label.
- 3.1.3 Mechanisms should be in place to determine whether an ADR qualifies for 15 day expedited reporting. When a case is found not reportable, justification is provided and documented.
- 3.1.4 For ADR reports that qualify for expedited reporting, the 4 minimum criteria (an identifiable reporter (source), an identifiable patient, a suspect product and an adverse reaction) for submitting a case are met.
- 3.1.5 Process should be in place for determining if a solicited report is to be submitted to Health Canada in an expedited fashion (within 15 days).
- 3.1.6 A qualified health care professional evaluates and assesses ADRs to determine whether the ADR qualifies for expedited 15-day reporting.
- 3.1.7 Reports of ADR cases from 2 or more sources
  - 3.1.7.1 A mechanism should be in place to identify ADR data that were reported to the MAH more than once.
  - 3.1.7.2 When similar reports are found, verifications should take place to determine if they are duplicate reports.
  - 3.1.7.3 Multiple copies of the same ADR reports should be nullified within the pharmacovigilance system and the record of nullification should be maintained, allowing for auditing of the nullified record in the future.
  - 3.1.7.4 Documented procedure and process should be in place describing when ADR reports may be nullified.
  - 3.1.7.5 Documentation related to nullified cases should be retained.
- 3.1.8 Additional information received for previously submitted ADR reports
  - 3.1.8.1 Upon receipt of follow-up information, ADR reports should be re-evaluated.
  - 3.1.8.2 Follow-up information received for previously submitted ADR reports must be sent to Health Canada within the prescribed timelines. 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.
  - 3.1.8.3 All reportable ADRs that have been upgraded to serious upon receipt of follow-up information are to be sent to Health Canada within the prescribed timelines



3.1.8.4 Rationale for changing the seriousness of an ADR report should be documented.

3.1.8.5 Process for seeking follow-up information and submitting it to Health Canada should be in place. All attempts to obtain follow-up information should be documented.

#### 4. Reporting of ADR data

##### 4.1 Market Authorization Holders

4.1.1 All ADRs that meet the requirements of the *Food and Drug Regulations* shall be reported to Health Canada in accordance with the *Food and Drug Regulations*.

##### 4.2 Importers

4.2.1 All suspected ADRs received should be sent to the MAH within an appropriate timeframe to allow for expedited reporting (if required), and should therefore be reported to Health Canada by the MAH in accordance with the requirements of the *Food and Drug Regulations*, if required.

4.2.2 Importers should follow-up with the MAH to ensure that ADRs have been assessed and submitted to the MHPD, if required.

#### 5. Literature Search

##### 5.1 Market Authorization Holders

5.1.1 The process, including but not limited to how the search is done, the database(s) used, and the periodicity of those searches describing the search in the literature should be written in a procedure.

5.1.2 Searches, on the marketed drug and active pharmaceutical ingredients, in published literature should be performed on a regular basis. Please refer to Section 4.1.3 of the MHPD document [Guidance Document for Industry - Reporting Adverse Reactions to Marketed Health Products](http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2011-guidance-directrice_reporting-notification/index-eng.php) ([http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/\\_guide/2011-guidance-directrice\\_reporting-notification/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2011-guidance-directrice_reporting-notification/index-eng.php)) for additional information.

5.1.3 ADRs found during literature searches should be classified according to their seriousness and expectedness. These assessments should be retained and be well documented.

5.1.4 ADR reports from the scientific and medical literature must be reported to Health Canada in accordance with the *Food and Drug Regulations*.

5.1.5 Results of the literature searches should be documented.

5.1.6 When literature search is performed by a third party, contractual agreements describing each party's responsibilities should exist.

#### Periodic Self-inspections

##### 6. Market Authorization Holders and Importers

6.1 A self-inspection program that covers all departments that may receive ADR reports or that are involved in pharmacovigilance activities may help to ensure compliance with the appropriate sections of the *Food and Drug Regulations* applicable to adverse drug reaction reporting. Self-inspection programs should be in place and should include but not be limited to the following;

- 6.1.1 A comprehensive written procedure that describes the functions of the self-inspection program.
  - 6.1.2 Periodic self-inspections that are carried out at defined frequencies, which are documented. If no ADRs have been received, the periodic self-inspections should include a simulation exercise.
  - 6.1.3 Reports on the findings of the self-inspections and on corrective actions. These reports should be reviewed by appropriate senior company management. Corrective actions should be implemented in a timely manner.
- 6.2 Periodic self-inspections should be conducted by personnel independent from the pharmacovigilance department and that are suitably qualified to perform and evaluate the inspections.

## **Personnel and Training**

### **7. Market Authorization Holders and Importers**

- 7.1 The individual in charge of the pharmacovigilance department should be qualified by pertinent training and experience relevant to their assigned responsibilities
- 7.2 The qualified health care professional;
  - 7.2.1 should have knowledge of all applicable sections of the *Food and Drug Regulations* related to the ADR reporting requirements, and of key pharmacovigilance activities performed as part of the MAH's pharmacovigilance system.
  - 7.2.2 should be responsible for establishing and managing/maintaining a system which ensures that information concerning all suspected ADRs that are reported to the personnel of the company and to medical representatives is collected and evaluated.
- 7.3 All personnel involved in pharmacovigilance activities, which may include customer service, sales representatives and receptionists, should have their specific duties recorded in a written description and have adequate authority to carry out their responsibilities.
- 7.4 All personnel involved in pharmacovigilance activities should be aware of the principles of pharmacovigilance that affect them, and all personnel should receive relevant training.
- 7.5 When responsible personnel are absent, qualified personnel should be appointed to carry out their duties and functions.
- 7.6 A qualified health care professional with adequate experience and education, as defined in 7.2, should be available to evaluate information in respect of a potential ADRs, assesses the seriousness, expectedness, and reportability of ADRs, and determine if the ADR report qualifies for expedited reporting (within 15 days) and if the report is to be included in the annual summary.
- 7.7 Training should be provided prior to implementation of new or revised procedures. Records of training should be maintained.
- 7.8 Consultants and contractors should have the necessary qualifications, training, and experience, as defined in 7.2 to fulfill their responsibilities.

## **Contractual Agreements**

### **8. Market Authorization Holders and Importer**

- 8.1 Contractual agreement should exist with every party that conducts pharmacovigilance activities, including third-party private label or other companies whose name is included in the product information or appears on the label and should include;
  - 8.1.1 who is responsible for determining if a complaint is a potential ADR,
  - 8.1.2 who is responsible to report ADR,
  - 8.1.3 who is responsible for preparing the ASR, including the critical analysis of the annual summary reports, and what process is utilized to conduct the critical analysis,
  - 8.1.4 who is responsible for conducting literature searches,
  - 8.1.5 processes by which an exchange of safety information, including timelines and regulatory reporting responsibilities, are taking place between the MAH and its partners (including, but not limited to, consultants and contractors).
  - 8.1.6 to notify other party if changes to procedures are made
- 8.2 In the case of foreign MAHs, the contractual agreement should specify to send known ADRs to the local MAH in a timely manner so as to promote compliance with regulatory reporting obligations.
- 8.3 In the case where the importer is responsible for the pharmacovigilance activities, the contractual agreement should specify that the foreign MAH is to send the ADR data to the importer in a timely manner.
- 8.4 All records (including, but not limited to, contractual agreements and safety data/ADR data) should be available on the premises of the MAH and the importer for auditing purposes.
- 8.5 When there is a transfer of market authorization/mergers, contractual agreement should exist between the previous MAH and the new one outlining each party responsibility.
- 8.6 Contractual agreement should be shared and signed off by each party.
- 8.7 Contractual agreement should be reviewed periodically in order to reflect current regulations and practices.

## **Validation of Computerized Systems**

- 9. Market Authorization Holders, Importer, and all parties involved in pharmacovigilance activities who use an electronic system
  - 9.1 Data of the validation of system(s) used for recording, evaluating, and tracking complaints and ADRs should be available.
  - 9.2 Computerized systems should be validated and systems are periodically and suitably backed up at predefined intervals.
  - 9.3 Any changes done to the system should be subject to a revalidation.

## Annual Summary Report and Case Reports - C.01.018

### Regulation

- (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 submits 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.

### Rationale

The annual summary report is an achievable mechanism for summarizing interval safety data, and for conducting an overall safety evaluation. MAHs are to conduct systematic analyses of safety data on a regular basis. The annual summary report can be used to identify safety signals or changes to what is known about the risks and benefits of the drug.

### Interpretation

**Note :** The MAH is responsible for this section of the *Food and Drug Regulations*. Importers who have been delegated the activities related to pharmacovigilance by the foreign MAH are required to meet all requirements outlined in the section below. Please note that all importers should have available evidence that the below requirements are met.

1. Written procedure for the preparation of the annual summary report (ASR) which should be in place and should include, but is not limited to the following:
  - 1.1 A requirement to submit the ASR upon request to Health Canada within the time frame specified by the Minister when the report is requested.
  - 1.2 The sections that should be included in the ASR as defined in Section 5.3 of the MHPD's guidance document entitled [Guidance Document for Industry - Reporting Adverse Reactions to Marketed Health Products](http://www.hc-sc.gc.ca/dhp-mpps/pubs/medeff/_guide/2011-guidance-directrice_reporting-notification/index-eng.php). ([http://www.hc-sc.gc.ca/dhp-mpps/pubs/medeff/\\_guide/2011-guidance-directrice\\_reporting-notification/index-eng.php](http://www.hc-sc.gc.ca/dhp-mpps/pubs/medeff/_guide/2011-guidance-directrice_reporting-notification/index-eng.php)).

1.3 Line-listing(s) of cases that are to be included in the ASR. Cases include ADRs:

- from unsolicited sources:
  - all domestic and foreign serious ADRs
  - all domestic and foreign non-serious unexpected ADRs
  - domestic cases of unusual failure in efficacy for new drugs
- from solicited sources and regulatory authority sources:
  - all domestic and foreign serious ADRs
  - domestic cases of unusual failure in efficacy for new drugs.

1.4 A requirement to prepare an ASR on an annual basis for each drug.

1.5 Documentation on what “selected 12-month period” is used for preparing the ASR.

**Note:** 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.

2. The MAH should 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 on an annual basis.
3. The MAH shall prepare an ASR of all information relating to ADRs and serious ADRs to the drug that it received or became aware of during the previous 12 months.
4. The ASR must contain a concise, critical analysis of the ADR and serious ADRs.
5. In preparing the ASR, the MAH shall assess any changes since the last annual summary report, and shall include its conclusions in this regard in the summary report. Any recommendation to take action (or not) must be included.
6. The MAH shall notify the Minister without delay, in writing, if in preparing the ASR the MAH concludes that there has been a significant change in what is known about the risks and benefits of the drug.
7. If the MAH has advised Health Canada that there is a significant change relating to its safe use, then records of the significant changes identified and records of the notification to the Health Canada must be available on file.
8. Requests for information from Health Canada should be maintained.
9. If the MAH chooses to use a third party to prepare the ASR, contractual agreements should be in place defining their respective responsibilities.
10. Annual summary report reviewed by Health Canada and for which comments were received by the MAH should be documented and changes should be implemented in subsequent summary report.
11. Signal detection
  - 11.1 Written procedure should be in place that adequately describes the way in which the MAH perform signal detection.
  - 11.2 Roles and responsibilities of each person involved in the signal detection process should be clearly identified and documented.
  - 11.3 The source of the information to include in the analysis and the method used for signal detection should be documented.

- 11.4 Actions taken based on the outcome generated from the signal detection activities should be documented adequately.
  - 11.5 Data regarding changes of what is known about the risks and benefits of the drug should be sent to Health Canada and should be documented.
12. Product Safety Information
- 12.1 The person who assesses ADR should have access to MAH's product safety information, including the company core data sheet (CCDS) or relevant Canadian labeling such as the product monograph, labeling standards, information approved for market authorization or the product label while preparing an ASR.
  - 12.2 Product information should be kept up to date.
  - 12.3 Records should be maintained of requests received from Health Canada to update product information documents, if applicable.
  - 12.4 Once a new safety issue has been identified drug product information should be updated, and procedures should be in place to facilitate timely submission of changes to ensure there is no undue delay in updating documents.

### **Issue-related Summary Report - C.01.019**

#### **Regulations**

##### **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.

#### **Rationale**

The issue-related summary report is a practical and achievable mechanism for summarizing a specific issue with a drug. That summary report contains information such as adverse drug reactions and serious ADRs to the drug and case reports of all or specified ADRs and serious ADRs to the drug that are known to the MAH.

## Interpretation

**Note:** The MAH is responsible for this section of the *Food and Drug Regulations*. Importers who have been delegated the activities related to pharmacovigilance by the foreign MAH are required to meet all requirements outlined in the section below. Please note that all importers should have available evidence that the below requirements are met.

1. Written procedure should be in place for the preparation of an issue-related summary report upon request from the Minister which includes but is not limited to:
  - 1.1 A concise, critical analysis of the ADRs and serious ADRs to the drug and case reports of all or specified ADRs and serious ADRs to the drug that are known to the MAH in respect of the issue that the Minister directs the MAH to analyse in the report.
  - 1.2 The maintenance of the issue-related summary report prepared by the MAH.

## Maintenance of Records - C.01.020

### Regulation

- (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.

### Rationale

Good documentation is an essential part of the quality assurance system and should therefore be related to all aspects of pharmacovigilance. Its aims are to ensure that the pharmacovigilance department has all the information necessary regarding the safety of a drug.

### Interpretation

**Note:** Importers who have been delegated the activities related to pharmacovigilance by the foreign MAH are required to meet all requirements outlined in the section below. Please note that all importers should have available evidence that the below requirements are met.

All relevant pharmacovigilance documents (such as associated records of actions taken or conclusions reached) and procedures are prepared by the relevant department. No changes are made without the approval of the qualified person in charge of the pharmacovigilance. Any alteration made to a document is signed and dated; the alteration permits the reading of the original information. Where appropriate, the reason for the change is recorded.

Any documentation requested for evaluation by Health Canada is provided in one of the official languages.

1. Market Authorization Holders and Importers
  - 1.1 Records of ADR reports and annual summary reports maintained by MAH are accessible when requested by Health Canada inspectors.
  - 1.2. Records shall be retained for a minimum of 25 years after the day on which they were created.
  - 1.3 A procedure should describe how ADR records are maintained, including the name of the filing system or electronic database which would facilitate the management of any such records in a reliable manner that allows for consistent retrieval.
  - 1.4 Complete records, such as documentation of decisions, documentation of follow-up and follow-up attempts, are available in ADR files.

- 1.5 All computer systems should have in place a security system that prevents unauthorized access and changes to the data.
- 1.6 A list of individuals who are authorised to access the system and make data changes should be maintained.
2. The MAH retains all ADR records and ASRs
3. The importer retains at the minimum the following documents (depending on their responsibilities):
  - 3.1 Evidence that ADRs that they received were sent to Health Canada;
  - 3.2 Evidence that summary reports were prepared on an annual basis, including date of issuance, summary and conclusions; and
  - 3.3 Any other evidence required to demonstrate that the MAH has met all requirements as presented in this document regarding ADR reporting.
4. A process should be established by the importer and the MAH for the accurate and timely retrieval of stored data or records from the pharmacovigilance system.

#### **New Drugs – C.08.007 (h) and C.08.008 (c)**

##### **Regulation**

###### **C.08.007 (h)**

Where a manufacturer has received a notice of compliance issued in respect of a new drug submission, an extraordinary use new drug submission, an abbreviated new drug submission, an abbreviated extraordinary use new drug submission or a supplement to any of those submissions, 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 (c)**

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.

##### **Rationale**

The safety and effectiveness of a new drug have not been established; therefore, MAH and importers should have a system in place that would allow them to provide to Health Canada, within prescribed time lines, the information related to any unusual failure in efficacy of a new drug product. The underlying principle is that if a 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.



## Interpretation

**Note:** The MAH is responsible for this section of the *Food and Drug Regulations*. Importers who have been delegated the activities related to pharmacovigilance by the foreign MAH are required to meet all requirements outlined in the section below. Please note that all importers should have available evidence that the below requirements are met.

1. The MAH should have systems and procedures in place to receive, evaluate and report to Health Canada within 15 days of the receipt of the information, any unusual failure in efficacy report of new drugs marketed in Canada.
2. The MAH should identify products with new drug status. Generally, a new drug is a drug which received a Notice of Compliance (NOC).
3. Every ADR report that meets the established criteria for reporting unusual failure in efficacy shall be submitted to Health Canada within the appropriate timeframe (within 15 days).
4. A qualified health care professional should evaluate potential cases of unusual failure in efficacy to determine if the case qualifies for expedited (15-day) reporting. These evaluations and assessments should be adequately documented.
5. The complete documentation of ADR reports of unusual failure in efficacy should be available for auditing purposes.
6. The complete documentation of ADR report of unusual failure in efficacy is retained for a minimum of 25 years after the day on which they were created.

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## Appendix A

### Glossary of Terms

The following definitions are provided to complement those already available under the glossary of terms in the current edition of the Canada Vigilance (MHPD) [Guidance Document for Industry - Reporting Adverse Reactions to Marketed Health Products](http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2011-guidance-directrice_reporting-notification/index-eng.php) ([http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/\\_guide/2011-guidance-directrice\\_reporting-notification/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2011-guidance-directrice_reporting-notification/index-eng.php)), the [Inspection Strategy for Good Pharmacovigilance Practices \(GVP\) for Drugs \(POL-0041\)](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/pol-41-gvp-eng.php) (<http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/pol-41-gvp-eng.php>), the [Risk Classification for Good Pharmacovigilance Practices \(GVP\) Observations \(GUI-0063\)](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0063_gvp-eng.php) ([http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0063\\_gvp-eng.php](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0063_gvp-eng.php)) and other related documents referenced in these documents.

**Adverse Drug Reaction (ADR)** - "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." (C.01.001. (1))

**Note:** For new drugs marketed in Canada, reports of unusual failure in efficacy are considered to be a type of adverse drug reactions (ADR) report.

**Annual Summary Report-** In accordance with the *Food and Drug Regulations*, the market authorization holder (MAH) must, on an annual basis and whenever requested by Health Canada, conduct a concise, critical analysis of the adverse drug reactions and serious adverse drug reactions to a drug and prepare a summary report in respect of the reports received during the previous twelve months or received during such period of time as Health Canada may specify. Annual summary reports may be submitted in the form of a Periodic Safety Update Report (PSUR) as defined by ICH E2C(R1) guideline.

**Drug** - "Any substance or mixture of substances manufactured, sold, or represented for use in (a) the diagnosis, treatment, mitigation, or prevention of a disease, a disorder, an abnormal physical state, or the symptoms thereof, in humans or animals, (b) restoring, correcting, or modifying organic functions in humans or animals, or (c) 'disinfection' in premises in which food is manufactured, prepared, or kept." (Section 2 of the *Food and Drugs Act*)

**Import** – "To import into Canada a drug for the purpose of sale" (C.01A.001)

**Manufacturer** - "Manufacturer" or "distributor" means a person, including an association or partnership, who under their own name, or under a trade-, design or word mark, trade name or other name, word or mark controlled by them, sells a food or drug. (A.01.010) Within the context of the GVP inspection program, MAH and importers are subject to GVP inspections as their name appears on the label and as such may receive ADRs.

**Market Authorization Holder** - For the purpose of this guidance document means the entity that holds the Notice of Compliance or the Drug Identification Number (DIN).

**New Drug** - "(a) a drug that contains or consists of a substance, whether as an active or inactive ingredient, carrier, coating, excipient, menstruum or other component, that has not been sold as a drug in Canada for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that substance for use as a drug; (b) a drug that is a combination of two or more drugs, with or without other ingredients, and that has not been sold in that combination or in the proportion in which those drugs are combined in that drug, for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that combination and proportion for use as a drug; or (c) a drug, with respect to which the manufacturer prescribes, recommends, proposes or claims a use as a drug, or a condition of use as a drug, including dosage, route of administration, or duration of action and that has not been sold for that use or condition of use in Canada, for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that use or condition of use of that drug." (C.08.001)  
Generally, if a NOC was issued for a drug, then that drug is considered to be a "new drug", regardless of how long it has been on the market.

**Notice of Compliance** - A notification, issued pursuant to paragraph C.08.004 (1) (a), indicating that a manufacturer has complied with sections C.08.002 or C.08.003 and C.08.005.1 of the *Food and Drug Regulations*. Notices of Compliance are issued to a manufacturer following the satisfactory review of a submission.

**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.

**Serious Adverse Drug Reaction** - "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." (C.01.001. (1))

**Serious Unexpected Adverse Drug Reaction** - "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." (C.01.001. (1))

**Signal Detection** - Many information sources may be combined to identify a signal or a preliminary indication of a product-related safety issue. Assessment consists of the scientific/medical review of multiple data sources to analyze risks and benefits, while determining the likelihood of the association between the reaction and the health product.

**Unusual Failure in Efficacy** - This has been considered an adverse drug reaction for many years under the Food and Drug Regulations. It applies to new drugs only. 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 judgment should be exercised by a qualified health care professional from the market authorization holder (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.

## Appendix B

### Associated Documents

1. [Food and Drugs Act](http://laws-lois.justice.gc.ca/eng/acts/F-27/)  
(<http://laws-lois.justice.gc.ca/eng/acts/F-27/>)
2. [Food and Drug Regulations](http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/index.html)  
([http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,\\_c.\\_870/index.html](http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/index.html))
3. [Compliance and Enforcement Policy \(POL-0001\)](http://hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/pol/pol_1_tc-tm_e.html)  
([http://hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/pol/pol\\_1\\_tc-tm\\_e.html](http://hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/pol/pol_1_tc-tm_e.html))
4. [Guidance Document for Industry – Reporting Adverse Reactions to Marketed Health Products \(2011\)](http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2011-guidance-directrice_reporting-notification/index-eng.php)  
([http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/\\_guide/2011-guidance-directrice\\_reporting-notification/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2011-guidance-directrice_reporting-notification/index-eng.php))
5. [ICH Harmonised Tripartite Guideline, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs E2C \(R1\) \(2005\).](http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html)  
(<http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>)
6. [Inspection Strategy for Good Pharmacovigilance Practices \(GVP\) for Drugs \(POL-0041\)](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/pol-41_gvp-eng.php)  
([http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/pol-41\\_gvp-eng.php](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/pol-41_gvp-eng.php))
7. [International Conference on Harmonisation, Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting \(ICH E2D\) \(2003\)](http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html)  
(<http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>)
8. [Risk Classification for Good Pharmacovigilance Practices \(GVP\) Observations \(GUI-0063\)](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0063_gvp-eng.php)  
([http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0063\\_gvp-eng.php](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0063_gvp-eng.php))