Health Canada Santé Canada

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

Risk Classification of Good Pharmacovigilance Practices (GVP) Observations

GUI-0063

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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.

Canada

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1.0 Purpose

To classify the observations noted during Good Pharmacovigilance Practices (GVP) (previously known as Post-Market Reporting Compliance) drug inspections to their risk.

To promote uniformity among the inspectors of Health Canada (Inspectorate Program) in the attribution of the rating following GVP inspections.

To inform the industry of the situations that Health Canada considers unacceptable and that will generate a non-compliant rating (NC) following a GVP inspection.

2.0 Background

During a GVP drug inspection, deviations from the *Food and Drug Regulations*, more specifically sections C.01.016 to C.01.020, and C.08.007 (h) and C.08.008 (c), and the current edition of the *Good Pharmacovigilance Practices (GVP) Guidelines (GUI-0102)* (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0102_gvp-eng.php) are noted by the inspector. These deviations appear as observations on the inspection Exit Notice. An assessment of these observations is then completed by the inspector who assigns a risk to each observation based on this guidance document. Subsequently, an overall compliance rating is attributed to the inspected site. The possible ratings are defined below:

> C (Compliant) - At the time of the inspection, the regulated party has demonstrated that the activities it conducts are in compliance with the *Food and Drugs Act* and its associated Regulations. A “C” rating does not mean that there are no observations or corrective actions required.
>
> NC (Non-Compliant) - At the time of the inspection, the regulated party has not demonstrated that the activities it conducts are in compliance with the *Food and Drugs Act* and its associated Regulations.

It is recognized that the evaluation of the conformity of manufacturers, which includes Market Authorization Holders (MAH) and importers in the context of this inspection program, with their regulatory responsibilities should be commensurate with the risk involved taking into account the nature and extent of the deviation. Nonetheless, generally, situations involving fraud, misrepresentation or falsification of drug safety data will generate a NC rating, irrespective of the category of products involved.

The assignment of a NC rating may have serious consequences for an establishment. These consequences may include the implementation of immediate corrective measures to the seizure and detention of drug products to the suspension and the cancellation of the marketing authorization; therefore, these situations of non-conformity have to be well defined, unambiguous and directly supported by the applicable sections of the *Food and Drug Regulations*.

3.0 Scope

The *Food and Drug Regulations* set forth regulatory requirements for manufacturers to report adverse drug reactions (ADR) and to report domestic unusual failure in efficacy of new drugs to Health Canada.

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.

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.

Appendix B of this document describes the observations related to each category of risk. Please note that the list of observations in the appendix is not exhaustive and additional observations may be added where appropriate.

The numbering system assigned to each section in Appendix B is a reference to the applicable regulations as per the current edition of the *Good Pharmacovigilance Practices (GVP) Guidelines (GUI-0102)* (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0102_gvp-eng.php).

4.0 Guide

4.1 Assignment of the Risk to an Observation

Whereas it is recognized that it is impossible to encompass every situation that may generate a risk, the following principles should be considered:

- The risk assigned will be in relation to the nature of the deviation as well as the number of occurrences.

- Where a Risk 2 observation is re-evaluated as a Risk 1 (Risk 2 observation with an upward arrow), this situation is immediately brought to the attention of the company's officials; proper explanation will be provided to the establishment.

4.2 Assignment of the Inspection Rating

The overall inspection rating assigned is based on the risk involved by taking into account the nature and extent of the deviations as well as the type of product involved and the impact on health and safety of the patient.

Generally, a NC rating is assigned when a Risk 1 observation is noted during an inspection.

Such a situation is immediately brought to the attention of the company's officials. The Inspectorate program management is notified in a timely manner as well.

Where in the opinion of the inspector the resulting products present a significant health risk, appropriate enforcement actions may be initiated.

A NC rating may also be assigned in the following situations:

- When numerous Risk 2 observations are noted during an inspection indicating that the company did not control its processes and operations sufficiently.

- When numerous occurrences of similar Risk 2 observations are noted during a GVP inspection indicating that the company did not have a system in place to provide for on-going process improvement.

- Repetition of many Risk 2 observations noted during previous inspections indicating that the company did not:
  - implement the corrective actions submitted following the previous inspection or
  - did not put in place adequate preventive actions in a timely manner to avoid recurrence of such deviations.

Generally, a C rating is assigned when Risk 2 observations are noted and in all situations where only Risk 3 observations are noted during an inspection.

4.3 Additional Guidance

When observations leading to a NC rating are made, the Inspection Exit Notice could be issued with a C rating if, during the inspection:

- the establishment immediately implements all necessary actions to resolve the cause(s) of the observation(s) leading to the NC rating and,
- sufficient assurance can be provided to prevent a recurrence.

In such instances, the risk assigned to the observation will remain the same.

If the management of the company wishes to dispute the results of the inspection report, they should contact the appropriate Inspectorate program regional manager.

5.0 Associated Documents

1. *Food and Drug Act*
   (http://laws-lois.justice.gc.ca/eng/acts/F-27/index.html)

2. *Food and Drug Regulations*
   (http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/index.html)

3. *Compliance and Enforcement Policy (POL-0001),*
   (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/pol/pol_1_tc-tm-eng.php)

4. *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)

5. ICH Harmonised Tripartite Guideline, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs E2C (R1) (2005)

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)

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

8. *Good Pharmacovigilance Practices (GVP) Guidelines (GUI-0102)*
   (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0102_gvp-eng.php)

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), the *Inspection Strategy for Good Pharmacovigilance Practices for Drugs (POL-0041)* (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/pol-4_gvp-eng.php) and the *Good Pharmacovigilance Practices (GVP) Guidelines (GUI-0102)* (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0102_gvp-eng.php) or 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: That, 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 (NOC) - 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 (NoC) are issued to a manufacturer following the satisfactory review of a submission.

Observation - A deviation from or deficiency based on the *Food and Drug Regulations* pertaining to reporting of adverse drug reactions (ADR) and unusual failure in efficacy of new drugs noted by an inspector during the inspection of a drug establishment that is confirmed in writing to the company in the Exit Notice. The observations are classified as "Critical", "Major" and "Other" and are assigned a risk classification, ranging from Risk 1 (critical) to Risk 2 (major) to Risk 3 (other).

> **Critical observation** (Risk 1):
> Observation of a critical deviation from the *Food and Drug Regulations* that describes a situation that may produce an immediate or latent health risk as a result of the absence of drug safety information. Observations that involve fraud, misrepresentation or falsification under the Food and Drugs Act and its associated Regulations of data are also considered critical.
>
> Refer to Appendix B for the list of observations which the Inspectorate program considers critical and which will be assigned a Risk 1.
>
> **Major observation** (Risk 2):
> Observation of a major deviation from the *Food and Drug Regulations* that describes a situation of incomplete drug safety information that may result in a latent health risk.
>
> Refer to Appendix B for the list of observations that are considered major and which will be assigned a Risk 2. Certain Risk 2 observations may be upgraded to Risk 1. These observations are indicated with an arrow **(↑)**; although it does not preclude other Risk 2 observations to be upgraded depending on the nature and the extent of the observation.
>
> **Other observation** (Risk 3):
> Observation that describes a deviation from the *Food and Drug Regulations* that is neither critical nor major.
>
> Observations that are neither critical nor major are considered as "other" and will be assigned a Risk 3. All Risk 3 observations could be upgraded to Risk 2 depending on the situation. Refer to Appendix B for the list.

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 analyse 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

Serious Adverse Drug Reaction Reporting C.01.017

Risk 1 (Critical) Observations

ADR Reporting

- None of the domestic serious expected or unexpected ADRs received are reported to Health Canada by the manufacturer.
- None of the foreign serious unexpected ADRs received are reported to Health Canada by the manufacturer.

Risk 2 (Major) Observations

ADR Reporting

Procedures and Processes

- Lack of or inadequate system for complaint handling.
- No written procedure for reporting any serious ADRs that occurred in Canada or any serious unexpected ADRs that occurred outside Canada within 15 days of receiving the information to Health Canada in accordance with the requirements of section C.01.017 of the *Food and Drugs Regulations*.
- Lack of systems and processes 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 unexpected ADRs, foreign serious unexpected ADRs, and domestic serious expected ADRs, as well as any follow-up information for initial case reports. **(↑)**

Receipt of ADR Data

- All suspected ADRs are not recorded and/or tracked appropriately.

Evaluation of ADR Data

- ADR reports are not properly coded.
- ADRs are not evaluated or assessed to determine whether they qualify for expedited 15-day reporting by a qualified health care professional.
- No documented rationale for nullifying case reports.
- Duplicate ADR case reports are nullified without the proper approval.
- Nullified reports are not maintained and are unavailable for auditing purposes.
- ADR reports are not re-evaluated upon receipt of follow-up information.

Reporting of ADR Data

- Less than the total number of domestic serious expected ADR reports and domestic serious unexpected ADR reports received by the MAH are reported to Health Canada. **(↑)**
- Less than the total number of foreign serious unexpected ADR reports received by the MAH are reported to Health Canada. **(↑)**
- Domestic serious ADRs are not reported within 15 calendar days of the receipt of the reports by the MAH. **(↑)**
- Foreign serious unexpected ADRs are not reported within 15 calendar days of the receipt of the reports by the MAH. **(↑)**

Literature Searches

- No written procedure describing the process to perform literature searches.

Periodic Self-Inspection

- Lack of or inadequate system for self-inspection program that covers all departments that may receive ADR reports or that are involved in pharmacovigilance activities.

Personnel and Training

- Individual in charge of the pharmacovigilance department is not qualified by pertinent experience and training. (↑)
- The individual who assesses the ADRs is not qualified. (↑)
- Delegation of responsibilities for pharmacovigilance activities to insufficiently qualified persons. (↑)
- Insufficient training for personnel involved in pharmacovigilance activities resulting in related GVP deviations.
- No training records available for the personnel in charge of receiving, evaluating and reporting ADRs.
- Consultant or contractor does not have necessary qualifications, training, and experience to advise on the subjects for which they are retained.

Contractual Agreements

- Lack of adequate contractual agreement in place to specify the processes by which an exchange of safety information, including timelines and regulatory reporting responsibilities, are taking place between the MAH/importer and its partners (For example: global headquarters).

Validation of Computerized Systems

- Computerized systems used for recording, evaluating, and tracking complaints and ADRs are not validated.

Risk 3 (Other) Observations

ADR Reporting

Procedures and Processes

- A comprehensive procedure and system for the receipt, evaluation and reporting of ADRs, the preparation of annual summary reports and the retention of all related data had not been formally defined and established.
- Systems and processes for the receipt, handling, evaluation and reporting of ADRs are deficient.

Evaluation of ADR Data

- The mechanism for determining whether a case qualifies for 15-day expedited reporting is inappropriately documented.
- Justification is not provided or documented for ADRs that do not qualify for 15-day expedited reporting upon evaluation.
- Follow-up information for initial case reports was not sought.

Reporting of ADR Data

- The decision-making process to determine the reportability of a case is not appropriately documented.
- Follow-up information for initial case reports was not submitted to Health Canada within the prescribed timelines.

Literature Searches

- Results of literature searches are not documented.

Personnel and Training

- Inadequate training records.
- Insufficient written training program.
- No organizational charts.

Contractual Agreements

- Incomplete contractual agreement for pharmacovigilance activities.

Validation of Computerized Systems

- Inadequate or incomplete validation of computerized systems.
- No periodic backups of the computerized systems.

Annual Summary Report and Case Reports C.01.018

Risk 1 (Critical) Observations

- The MAH did not notify Health Canada in writing of a significant change in what is known about the risks and benefits of the drug in preparing the annual summary report.

Risk 2 (Major) Observations

- Annual summary reports (ASR) of domestic serious ADRs and foreign serious unexpected ADRs are not maintained by the MAH.
- Annual summary reports of domestic serious ADRs and foreign serious unexpected ADRs are not prepared by the MAH. (↑)
- When requested by Health Canada, case reports and annual summary reports have not been submitted within the time period specified by Health Canada.
- No written procedure for the preparation of the annual summary report.
- Changes recommended by Health Canada to the MAH following their review of previous ASR(s) were not documented and/or implemented in subsequent annual summary reports.
- No contractual agreement with the third party responsible for preparing the annual summary reports.
- Lack of or inadequate written procedure that describes the way in which the MAH performs signal detection.
- Obsolete product safety information used for the assessment of expectedness.

Risk 3 (Other) Observations

- The MAH has not included in the annual summary reports line-listing(s) of the following cases that were received:
  - from unsolicited sources:
    - all domestic and foreign serious ADRs
    - all ADRs 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.
- Incomplete annual summary reports.
- Incomplete or inadequate procedure describing how annual summary reports are prepared.

Issue-related Summary Report C.01.019

Risk 1 (Critical) Observations

- The MAH has not submitted the issue-related summary report upon receiving the request from Health Canada.

Risk 2 (Major) Observations

- No written procedure for the preparation of an issue-related summary report when a request is received from Health Canada.

Risk 3 (Other) Observations

- Incomplete or inadequate procedure describing how an issue-related summary report is to be prepared when requested by Health Canada.

Maintenance of Records C.01.020

Risk 1 (Critical) Observations

- Evidence of falsification or misrepresentation of records.
- No records of ADR reports were accessible for auditing purposes.

Risk 2 (Major) Observations

- Lack of or inadequate procedure describing how ADR records are maintained.
- Records are not retained for a minimum of 25 years after the day on which they were created.
- Not all records of serious ADR reports and annual summary reports are maintained by the MAH.
- Not all records of serious ADR reports and ASR were accessible for auditing purposes.
- Lack of or incomplete records of complaints.

- No restricted access to ADR records.

Risk 3 (Other) Observations

- Incomplete records in ADR files.

New Drugs C.08.007 and C.08.008

Risk 1 (Critical) Observations

- No records of reports of domestic unusual failure in efficacy of new drugs were accessible for auditing purposes.
- None of the reports of the domestic unusual failure in efficacy of new drugs received are reported to Health Canada by the MAH.

Risk 2 (Major) Observations

- Not all records of domestic unusual failure in efficacy of new drugs were accessible for auditing purposes.
- Less than the total number of reports of domestic unusual failure in efficacy of new drugs received by the MAH were reported to Health Canada. (↑)
- Domestic cases of unusual failure in efficacy of new drugs are not reported within 15 calendar days of the receipt of the reports by the MAH. (↑)
- Lack of or inadequate systems and procedures in place for the receipt, evaluation and reporting to Health Canada within 15 days of the receipt of the information, domestic cases of unusual failure in efficacy of new drugs marketed in Canada.
- Complete documentation of ADR reports of unusual failure in efficacy is not retained for a minimum of 25 years after the day on which they were created.
- Suspected domestic cases of unusual failure in efficacy are not evaluated or assessed to determine whether they qualify for expedited 15-day reporting.
- Suspected domestic cases of unusual failure in efficacy are not evaluated by a qualified health care professional.

Risk 3 (Other) Observations

- Assessments of suspected domestic cases of unusual failure in efficacy of new drugs are not appropriately documented.