

Risk classification guide for good pharmacovigilance practices (GVP) observations (GUI-0063): Overview

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Overview

Risk and Rating

Sample observations

Glossary

Related Links

Disclaimer: This document does not constitute legislation. If there is any inconsistency or conflict between the legislation and this document, the legislation takes precedence. This document is an administrative document that is intended to help the regulated party comply with the legislation and the applicable administrative policies.

On this page

- [Purpose](#)
- [Scope](#)
- [Introduction](#)

Purpose

This guidance document helps ensure consistency among Health Canada inspectors during good pharmacovigilance practices (GVP) inspections as discussed in the [Good pharmacovigilance practices \(GVP\) guidelines \(GUI-0102\)](#) when:

- classifying GVP observations according to risk
- assigning an overall inspection rating to an inspection

This guidance document also informs manufacturers or market authorization holders (MAHs) of the scenarios that are considered unacceptable. These scenarios may result in:

- a non-compliant (NC) rating **and/or**
- compliance and enforcement actions
 - in accordance with the [Compliance and enforcement policy \(POL-0001\)](#)

Scope

These guidelines apply to all persons (individuals and companies) involved in post-market pharmacovigilance activities of the manufacturer or MAH.

These guidelines apply to these human drugs:

- pharmaceutical drugs, prescription and non-prescription,
- biologics set out in Schedule D of the act, including:
 - biotechnology products,
 - vaccines,
 - fractionated blood products,
- radiopharmaceuticals set out in Schedule C of the act,
- medical gases.

These guidelines do not apply to:

- sperm and ova
- medical devices
- veterinary products
- natural health products
- cells, tissues and organs
- whole blood and blood components
- biocides (surface disinfectant and surface sanitizers)

Although these product lines are out of scope of this guide, vigilance requirements may still apply. It is your responsibility as the manufacturer or MAH to ensure compliance with the requirements set out within the act and regulations for your products.

Introduction

During a GVP inspection, we note deviations from the [Food and Drugs Act](#) (act), [Food and Drug Regulations](#) (regulations), the [Good pharmacovigilance practices \(GVP\) guidelines \(GUI-0102\)](#) and other applicable guidance documents.

These deviations appear as observations in the inspection exit notice provided to the manufacturer or MAH.

This guidance document will explain how we assign a risk to observations and how we assign an overall inspection rating. It will also provide sample observations that we may note during an inspection.

Risk classification guide for good pharmacovigilance practices observations (GUI-0063): Risk and Rating

Overview	Risk and Rating	Sample observations
Glossary	Related Links	

On this page

- [Assigning risks to observations](#)
- [Assigning an overall inspection rating](#)

Assigning risks to observations

We assign a risk classification to each observation where there is a deviation from the act, regulations, and GVP requirements set out in our guidance document. Risk classifications range from 1 for “critical”, to 2 for “major” and 3 for “other”.

- **Critical observation (Risk 1):** describes a deviation that
 - is likely to pose an immediate or latent risk to the safety of patients or public health or
 - involves fraud, deception, misrepresentation or falsification of processes, records, or data.
- **Major observation (Risk 2):** describes a deviation that
 - may result in a potential risk to the safety of patients or public health.
 Note: some Risk 2 observations **may be** upgraded to Risk 1, these are indicated with an arrow (↑)
- **Other observation (Risk 3):** describes a deviation that
 - is neither critical nor major
 - is a departure from the GVPs that would not be expected to affect the safety of patients or public health.
 Note: any Risk 3 observation can be upgraded to Risk 2.

This guidance document outlines [examples of general observations](#) that are considered critical (Risk 1), major (Risk 2), and other (Risk 3). However, it is impossible to foresee every situation that may generate a risk. We may assign the risk rating depending on a variety of factors such as:

- product risk
 - factors that may indicate higher risk such as:
 - route of administration
 - sterile products
 - vulnerable population groups

- products with a risk management plan
- terms and conditions (T&C) attached to the drug identification number (DIN)

- extent of impact
- number of occurrences
- recurrence of the deficiencies
- nature and severity of the observation

Cited observations in the inspection exit notice will contain the specifics or context, as required.

An observation would be considered a repeat observation if:

- it is the same as or similar to any past observation
- there is a reasonable expectation that the corrective measure(s) for the past observation would have prevented the GVP deficiency from occurring again

All observations recorded in the inspection report require corrective actions and preventive actions (CAPA), regardless of the overall inspection rating attributed to the inspection. Observations requiring immediate or expedited corrective actions will be identified for the regulated party. This includes Risk 1 observations, or Risk 1 observations that were upgraded from a Risk 2 (Risk 2 observation with an arrow (↑)).

Assigning an overall inspection rating

We consider the risk involved when assigning the overall inspection rating, taking into account the:

- nature and extent of the deviations
- type of product involved
- impact on the patient's health and safety, as well as risk to public health

The possible overall inspection ratings are:

- **"C" (Compliant):** At the time of the inspection, the regulated party has demonstrated that the activities it conducts comply with the act and regulations.
- **"NC" (Non-compliant):** At the time of the inspection, the regulated party has not demonstrated that the activities it conducts comply with the act and regulations.

Generally, a compliant "C" rating will be assigned where:

- few Risk 2 observations, focused on isolated issues, are noted
- only Risk 3 observations are noted

Generally, a non-compliant "NC" rating will be assigned when:

- a Risk 1 observation is noted during an inspection
- numerous Risk 2 observations are noted during an inspection

- indicates the company does not control its processes and operations sufficiently
- Risk 2 observations identifying overarching systematic issues

When an “NC” rating is under consideration or the rating needs further review, we will review the inspection exit notice for quality assurance purposes before issuing the final report.

We will outline the methods of dispute in the letter accompanying the exit notice should the manufacturer or MAH wish to contest the results of the inspection report or the final rating.

Based on the nature of the deficiencies observed and where there is a significant health risk, we may initiate compliance and enforcement actions according [Compliance and enforcement policy for health products \(POL-0001\)](#) to mitigate the risk and correct any non-compliance.

Risk classification guide for good pharmacovigilance practices observations (GUI-0063): Sample observations

Overview	Risk and Rating	Sample observations
Glossary	Related Links	

On this page

- [Pharmacovigilance system](#)
- [Terms and conditions](#)
- [Serious adverse drug reaction \(ADR\) reporting](#)
- [Annual summary report \(ASR\) and case reports](#)
- [Issue-related summary report \(IRSR\)](#)
- [Maintenance of records](#)
- [Foreign actions](#)
- [Unusual failure in efficacy](#)
- [Label updates](#)

The following are sample observations that we may note during an inspection. We may cite other observations where appropriate, and this is not intended to be an all-inclusive list.

Pharmacovigilance system

This section on pharmacovigilance system is relevant to any regulations that apply. The regulation(s) impacted by the identified deficiency will be cited.

Risk 2 (major) observations

Self-inspection:

- Lack of or inadequate self-inspection program.
- Self-inspection program records were not maintained.

Validation of computerized systems:

- A computerized system used to manage pharmacovigilance data was not validated.

Personnel and training:

- The personnel conducting key pharmacovigilance activities was not sufficiently qualified or trained.

Contractual agreements:

- Lack of or inadequate contractual agreements in place with third-party affiliates or contracted vendors that may impact the safety of patients or public health.

Risk 3 (other) observations**Deviation, change control, business continuity:**

- Deviations have not been properly documented.
- Inadequate management on deviations.
- Inadequate change control system.
- Inadequate business continuity plan.

Self-inspection:

- Frequency of self-inspection is not justified by a risk-based strategy.

Validation of computerized systems:

- No periodic back-ups of the computerized systems.
- Inadequate system validation or re-validation.
- Incomplete documentation to evaluate the need for validation or re-validation.

Personnel and training:

- Pharmacovigilance personnel were not trained before carrying out the respective duties.
- A qualified and trained alternate was not identified for times when key pharmacovigilance personnel were absent.
- The job description for pharmacovigilance personnel was not updated to reflect all pharmacovigilance responsibilities.
- Inadequate or lack of organizational charts.
- Inadequate training records.

Contractual agreements:

- Incomplete details on a contractual agreement for pharmacovigilance activities that was not expected to impact the safety of patients or public health.

Terms and conditions

C.01.014.21 of the regulations

(1) The Minister may, at any time, impose terms and conditions on a drug identification number assigned for a Class B opioid or amend those terms and conditions.

(1.1) The Minister may, at any time, impose terms and conditions on a drug identification number assigned for a public health emergency drug or amend such terms and conditions if

- (a) a notice of compliance was issued under section C.08.004 in respect of
 - (i) a new drug submission that was filed for the public health emergency drug under section C.08.002 and contains the statement referred to in paragraph C.08.002(2.1)(a), or
 - (ii) a supplement to any new drug submission that was filed for the public health emergency drug under section C.08.003 and contains the statement referred to in paragraph C.08.003(5)(a); or
- (b) a notice of compliance was issued under section C.08.004 in respect of one of the following submissions or supplements that was filed in respect of the public health emergency drug on the basis of a direct or indirect comparison to another public health emergency drug referred to in paragraph (a):
 - (i) a new drug submission under section C.08.002,
 - (ii) an abbreviated new drug submission under section C.08.002.1, or
 - (iii) a supplement to a new drug submission or abbreviated new drug submission under section C.08.003.

(2) The Minister shall notify, in writing, the manufacturer to whom a document was issued under subsection C.01.014.2(1) that sets out the drug identification number of any terms and conditions imposed on the drug identification number and of any amendment to those terms and conditions.

(3) The following definitions apply in this section.

Class B opioid means a drug set out in Part B of the List of Opioids, published by the Government of Canada on its website, as amended from time to time. (opioïde de catégorie B)

public health emergency drug has the same meaning as in section C.08.001.1. (drogue pour urgence de santé publique)

Risk 2 (major) observations

- The T&C was not implemented or fulfilled. (↑)
- The T&C was only partially implemented or fulfilled. (↑)
- The T&C was not implemented or fulfilled in a timely manner. (↑)
- There was no system or process to implement the T&C.
- Inadequate procedure that enable T&C implementation.

Risk 3 (other) observations

- Incomplete process related to the T&C.

Serious adverse drug reaction reporting

C.01.017 of the regulations

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.

Risk 1 (critical) observations

Submission of ADR data:

- None of the domestic serious expected or unexpected adverse drug reactions (ADRs) were submitted to us.
- None of the foreign serious unexpected ADRs were submitted to us.

Risk 2 (major) observations

Receipt, handling, documenting, and processing of ADR data:

- ADRs were inappropriately nullified or invalidated. (↑)
- Lack of or inadequate system and processes to receive, handle, document, and process ADRs in a timely manner.
- ADRs were not properly coded.
- ADRs were not verified against duplication that exist in your pharmacovigilance database.

Evaluation of ADR data:

- Lack of or inappropriate evaluation of ADRs.
- ADRs were not re-evaluated upon receipt of follow-up information.
- Lack of or inadequate system and processes to evaluate ADRs in a timely manner.

Submission of ADR data:

- Missed or late ADR submissions. (↑)
- Clinically significant/relevant follow-up information was not re-submitted to us in a timely manner.
- Lack of or inadequate system and processes to submit ADRs in a timely manner.

Risk 3 (other) observations

- Incomplete procedures on managing ADRs.
- Incomplete documentation of ADRs.
- Lack of or inadequate follow-up on ADRs.

Annual summary report and case reports

C.01.018 of the regulations

- (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.

Risk 1 (critical) observations

Notification to the Minister:

- The manufacturer did not notify us, without delay, in writing of a significant change in what is known about the risks and benefits of the drug as soon as one has been identified and assessed when preparing the ASR.

Risk 2 (major) observations

ASR preparation:

- Incomplete ASR to enable critical analysis of the drug. (↑)
For example:
 - signal management was performed on an incomplete set of data
 - incomplete information that precluded meaningful and critical analysis
 - missing information or section(s) expected by the PBRER, PSUR, or non-standardized format
- The manufacturer did not prepare and maintain ASR(s) for the drug it sells. (↑)

- The ASR identified safety finding or changes to risks and benefits of the drug but the manufacturer did not (↑):
 - address or evaluate on the need to update the product label, or
 - address or evaluate on the need to introduce or update risk mitigation strategies, or
 - address or evaluate whether there has been a significant change in what is known about the risks and benefits of the drug.
- ASR was not prepared within the expected timeline.
- Lack of or inadequate system and processes for preparing ASRs and may impact the critical analysis of the drug.

Notification to the Minister:

- Lack of or inadequate system and processes to inform the Minister about a significant change without delay.

ASR submission:

- The ASR and case reports, when requested by us, have not been submitted within the specified time period.

Signal management:

- Lack of or inadequate system and processes for signal management or environmental scanning that may impact the critical analysis of the drug.
- Signal management or environmental scanning has never been conducted.
- Signal management or environmental scanning was not conducted according to established procedures on consistent occasions.

Risk 3 (other) observations

ASR preparation

- Cases of non-serious ADRs were missed when preparing an ASR.
- There were incomplete details about an ASR that was not expected to impact the critical analysis of the drug.
- Incomplete procedures on ASR.

Signal management:

- Incomplete documentation on signal management or environmental scanning.
- Incomplete procedures on signal management or environmental scanning.

Issue-related summary report

C.01.019 of the regulations

- (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 only specify a period that is less 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.

Risk 1 (critical) observations

- The manufacturer has not submitted the issue-related summary report (IRSR).

Risk 2 (major) observations

- The IRSR was performed on an incomplete set of data. (↑)
- Lack of or inadequate system and processes for preparing and submitting IRSRs that may impact the assessment of the drug.

Risk 3 (other) observations

- Incomplete procedures related to IRSR.

Maintenance of records

C.01.020 of the regulations

- (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.

Risk 1 (critical) observations

- Evidence showed that records have been falsified or misrepresented or inappropriately destroyed.
- No records pertaining to the regulations C.01.017 to C.01.019 were accessible for inspection purposes.

Risk 2 (major) observations

- Records were not maintained for 25 years. (↑)
- Inadequate data management practices to ensure data accuracy and data integrity.
- Lack of or inadequate system and processes on how data should be acquired, modified, reviewed and maintained for 25 years.
- Nullified or invalidated ADR reports were not documented properly or were unavailable for inspection.

Risk 3 (other) observations

- Records about the company's organization charts or job descriptions were incomplete.
- Incomplete procedures on record maintenance.

Foreign actions

C.01.050 of the regulations

- (1) This section applies to a holder of 1 or more of the following therapeutic product authorizations:
 - (a) a drug identification number that has been assigned under subsection C.01.014.2(1); and
 - (b) a notice of compliance that has been issued under section C.08.004 or C.08.004.01.
- (2) The holder of a therapeutic product authorization in respect of a drug that is part of a class of drugs set out in subsection (4) shall provide the Minister with information in respect of any serious risk of injury to human health that the holder receives or becomes aware of and that is relevant to the safety of the drug, regarding
 - (a) risks that have been communicated by any foreign regulatory authority that is set out in Part A of the List of Foreign Regulatory Authorities for the Purposes of Section C.01.050 of the *Food and Drug Regulations*, published by the Government of Canada on its website, as amended from time to time, or by any person who is authorized to manufacture or sell a drug within the jurisdiction of such an authority, and the manner of the communication;
 - (b) changes that have been made to the labelling of any drug and that have been communicated to or requested by any foreign regulatory authority that is set out in Part B of the list referred to in paragraph (a); and
 - (c) recalls, reassessments and suspensions or revocations of authorizations, including licences, in respect of any drug, that have taken place within the jurisdiction of any foreign regulatory authority that is set out in Part C of the list referred to in paragraph (a).
- (3) The information shall be provided to the Minister within 72 hours after the holder receives or becomes aware of it, whichever occurs first.
- (4) The classes of drugs are
 - (a) prescription drugs;

(b) drugs that are required to be sold under a prescription by Part G, the *Benzodiazepines and Other Targeted Substances Regulations* or the *Narcotic Control Regulations*; and

(c) drugs that are permitted to be sold without a prescription but that are to be administered only under the supervision of a practitioner.

(5) Despite subsection (2), a holder of a therapeutic product authorization who provided information in accordance with

(a) paragraph (2)(a) is not required to provide the same information again under that paragraph in the case where the holder receives or becomes aware of that information in respect of a foreign regulatory authority or person referred to in that paragraph; or

(b) paragraph (2)(b) or (c) is not required to provide the same information again under that paragraph in the case where the holder receives or becomes aware of that information in respect of a foreign regulatory authority referred to in that paragraph.

(6) In this section, foreign regulatory authority means a government agency or other entity outside Canada that has a legal right to control the manufacturing, use or sale of drugs within its jurisdiction and that may take enforcement action to ensure that drugs marketed within its jurisdiction comply with the applicable legal requirements.

Risk 1 (critical) observations

- The MAH was aware of a foreign action related to serious risk of injury to human health but did not notify us.

Risk 2 (major) observations

- The MAH did not notify us of foreign actions in a timely manner. (↑)
- Lack of or inadequate system and processes to ensure timely notification of foreign actions.
- There was no monitoring of foreign actions.
- Monitoring of foreign actions was not conducted according to the established procedures on consistent occasions.

Risk 3 (other) observations

- Incomplete documented evidence to show that periodic searches have been conducted to identify possible foreign actions.
- Incomplete procedures related to foreign actions.

Unusual failure in efficacy

C.08.007 (1)(h), C.08.008 (c) of the regulations

C.08.007

- (1) 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

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) a summary of a record respecting any information referred to in paragraph C.08.007(1)(g) or (h) within 15 days after the day on which the manufacturer established the record.

Risk 1 (critical) observations

- None of the domestic unusual failure in efficacy (UFIE) reports of new drugs received were submitted to us.

Risk 2 (major) observations

- Missed or late UFIE submissions. (↑)
- UFIEs were inappropriately nullified or invalidated. (↑)
- Lack of or inadequate system and processes to receive, handle, document, process, evaluate, and submit UFIEs in a timely manner.
- UFIEs were not properly coded.
- UFIEs were not verified against duplication that exist in your pharmacovigilance database.
- Lack of or inappropriate evaluation of UFIEs.
- UFIEs were not re-evaluated upon receipt of follow-up information.
- Clinically significant/relevant follow-up information was not re-submitted to us in a timely manner.

Risk 3 (other) observations

- Incomplete procedures on managing UFIEs.
- Incomplete documentation of UFIEs.
- Lack of or inadequate follow-up on UFIEs.

Label update

C.08.003 of the regulations

C.08.003

- (1) Despite section C.08.002, no person shall sell a new drug in respect of which a notice of compliance has been issued to the manufacturer of that new drug and has

not been suspended under section C.08.006, if any of the matters specified in subsection (2) are significantly different from the information or material contained in the new drug submission, extraordinary use new drug submission, abbreviated new drug submission or abbreviated extraordinary use new drug submission, unless (a) the manufacturer of the new drug has filed with the Minister a supplement to that submission; (b) the Minister has issued a notice of compliance to the manufacturer of the new drug in respect of the supplement; and (c) the notice of compliance in respect of the supplement has not been suspended under section C.08.006.

Risk 1 (critical) observations

- Product label was not updated to contain new safety information related to a significant change in what is known about the risks and benefits of a drug.

Risk 2 (major) observations

- Product label was not updated to contain new safety information in a timely manner.
- Lack of or inadequate system and processes on label update that may impact the safety of patients and public health.
- The MAH was aware of a serious risk of injury to human health that was significantly different from the product label but did not communicate with us or submit the change in a timely manner. (↑)

Risk 3 (other) observations

- Incomplete procedures on label update.
- Incomplete documentations related to communications on label updates.

Risk classification guide for good pharmacovigilance practices observations (GUI-0063): Glossary

[Overview](#)[Risk and Rating](#)[Sample observations](#)[Glossary](#)

On this page

- [Acronyms](#)
- [Glossary](#)

Acronyms

ADR: adverse drug reaction

AE: adverse event

ASR: annual summary report

C: compliant

DIN: Drug Identification Number

ICH: International Council for Harmonisation

IRSR: issue-related summary report

GVP: good pharmacovigilance practices

MAH: market authorization holder

NC: non-compliant

NOC: notice of compliance

RMP: risk management plan

Glossary

These definitions explain how terms are used in this document. If there is a conflict with a definition in the [Food and Drugs Act](#) (act) or the [Food and Drug Regulations](#) (regulations), the definition in the act or regulations prevails.

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) of the regulations)

The phrase “response to a drug” means that a causal relationship between a drug and an adverse event is at least a reasonable possibility (refer to the ICH E2A guideline). A reaction, in contrast to an event, is characterised by the fact that a causal relationship between the drug and the occurrence is suspected.

For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse drug reaction.

(ICH E2D (R1))

Adverse event (AE):

An adverse event is any untoward medical occurrence in a patient administered a health product and which does not necessarily have to have a causal relationship with this health product. 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 health product, whether or not considered related to this health product.

(adopted from ICH E2D (R1))

Annual summary report (ASR):

A comprehensive assessment of all known safety information for a marketed drug. It provides an update on the worldwide safety profile at defined intervals throughout the post-authorization life cycle of the drug or product.

Case report:

A detailed record of all relevant data associated with the use of a drug in a subject.

(C.01.001(1) of the regulations)

Compliant (C):

At the time of the inspection, the regulated party has demonstrated that the activities it conducts comply with the act and regulations.

Drug:

Any substance or mixture of substances manufactured, sold or represented for use in:

- the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,
- restoring, correcting or modifying organic functions in human beings or animals, or
- disinfection in premises in which food is manufactured, prepared or kept;

(Section 2 of the act)

Drug Identification Number (DIN):

A computer-generated 8 digit number assigned by us to a drug upon market authorization under subsection C.01.014.2 (1) of the regulations. It identifies each drug under the regulations, sold in a dosage form in Canada, and is located on the package label of prescription and non-prescription drugs that have been evaluated and authorized for sale in Canada.

A DIN uniquely identifies the following characteristics:

- Product Name
- Manufacturer Name
- Active Ingredient(s)
- Strength of Active Ingredient(s)
- Dosage Form
- Route(s) of Administration
- Species (for veterinary drugs only)

Issue-related summary reports (IRSR):

A concise, critical analysis of a specific safety or effectiveness issue, based on an analysis of adverse reaction reports.

Label:

label includes any legend, word or mark attached to, included in, belonging to or accompanying any food, drug, cosmetic, device or package;

(section 2 of the act)

Label includes:

- Labels affixed to the container or packaging of the drug
- Any separate package inserts
- Prescribing Information
- Fact sheets
- Consumer information/patient medication information (i.e., patient leaflets)
- Patient diaries
- Product Monograph, or
- Other material containing information specific to the drug

Package labels generated by the manufacturer may be included in the packaging or supplied to the consumer at the time of dispensing.

Manufacturer:

A person, including an association or partnership, who under their own name, or under a trade-, design or wordmark, tradename or other name, word or mark controlled by them, sells a food or drug.

(A.01.010 of the regulations)

Where the market authorization holder (MAH) is the entity that sells a drug under a name it controls, the MAH would be considered the manufacturer. For this reason, MAHs are subject to good pharmacovigilance practices (GVP) inspections as they sell a drug under their own name, or a trade-, design or wordmark, tradename or other name, word or mark that they control. However, other scenarios may apply and each scenario will need to be assessed on a case-by-case basis.

Market authorization holder (MAH):

For the purpose of this guidance document, the entity that holds the notice of compliance (NOC) or the drug identification number (DIN) is the MAH.

New drug:

A drug that:

- a. 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. is a combination of 2 or more drugs, with or without other ingredients, and 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. 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 of the regulations)

In general, if a notice of compliance was issued for a drug, it is considered to be a "new drug", regardless of how long it has been on the market.

Non-compliant (NC):

At the time of the inspection, the regulated party has not demonstrated that the activities it conducts comply with the act and regulations.

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, C.08.002.1 or C.08.003 and

C.08.005.1 of the regulations. NOCs are issued to a manufacturer following the satisfactory review of a submission.

Observation:

A deviation from or deficiency based on the regulations noted by an inspector during a good pharmacovigilance inspection that is confirmed in writing in the final inspection exit notice. The observations are classified as "critical" (risk 1), "major" (risk 2) and "other" (risk 3).

Pharmacovigilance:

The science and activities for detecting, assessing, understanding and preventing adverse events or any other drug-related problems.

"Routine pharmacovigilance measures" (or "activities") are activities or methods that are sufficient for post-approval safety monitoring of drugs where there are no special concerns.

Examples include:

- monitoring the safety profile of the drug through signal detection activities
- preparing reports, such as PSURs, for regulatory authorities

"Additional pharmacovigilance measures" (or "activities") are activities or methods that are used to address products with special safety concerns that cannot be sufficiently addressed by routine measures. These special safety concerns include the need for additional data to:

- better characterize risks or
- evaluate the effectiveness of additional risk minimization measures

Examples include safety studies or registries.

Risk management plan (RMP):

A document that describes:

- a set of pharmacovigilance measures and interventions to identify and characterize risks associated with the drug and to prevent or reduce those risks and address uncertainties and
- the assessment of the effectiveness of those interventions

Serious adverse drug reaction:

A noxious and unintended response to a drug that occurs at any dose and:

- 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) of the regulations)

Serious adverse event/adverse drug reaction:

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening
 - NOTE: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe);
- requires inpatient hospitalization or results in prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is a medically important event or reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

Examples of such events which may occur following the use of a health product 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 dependency or substance use disorder.

(adopted from ICH E2D (R1))

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) of the regulations)

Signal:

A signal is information that:

- arises from 1 or multiple sources
 - including observations and experiments
- suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events (adverse or beneficial).

(adopted from CIOMS Cumulative Pharmacovigilance Glossary: Version 1.0)

Signal management:

A set of activities such as signal detection and evaluation to determine whether a signal represents a risk which may warrant further assessment, communication, or other risk minimization actions in accordance with the medical importance of the issue.

(adopted from CIOMS Cumulative Pharmacovigilance Glossary: Version 1.0)

Significant change:

Refer to the Guidance on preparing and submitting summary reports for marketed drugs and natural health products.

Unusual failure in efficacy (UFIE):

Refer to the Reporting adverse reactions to marketed health products – Guidance document for industry.

Unexpected ADR:

An AR is considered unexpected when its nature, severity, specificity or frequency is either not identified, or is not consistent with the terms or description used in the Canadian product labelling, such as the:

- product monograph
- labelling standards
- information approved for market authorization
- product label

(adopted from ICH E2D (R1))

Risk classification guide for good pharmacovigilance practices observations (GUI-0063): Related links

[Overview](#)[Risk and Rating](#)[Sample observations](#)[Glossary](#)[Related links](#)

Laws and regulations

- [Food and Drugs Act \(act\)](#)
- [Food and Drug Regulations \(regulations\)](#)

Health Canada Quality Documents

Policies

- Inspection strategy for good pharmacovigilance practices (GVP) for drugs (POL-0041)
- [Compliance and enforcement policy for health products \(POL-0001\)](#)

Guidance Documents

- Good pharmacovigilance practices (GVP) guidelines (GUI-0102)

Other Guidance Documents and Databases

- [The drug and health products inspections database \(DHPID\)](#)
- [Compliance and enforcement policy framework](#)