

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

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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.

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1.1 Purpose

This guide is for manufacturers or market authorization holders (MAH), who sell drugs and are responsible for post-market pharmacovigilance activities and good pharmacovigilance practices (GVP). When you sell a drug under a name you control, you meet the definition of a manufacturer.

Health Canada performs GVP inspections to assess your compliance with the following post-market pharmacovigilance and GVP requirements outlined in the [Food and Drug Regulations](#) (regulations).

- C.01.014.21
- C.01.016 to C.01.020
- C.01.050
- C.08.007(1)(h)
- C.08.008 (c)
- C.08.003

It is important to implement GVP to monitor and assess the safety and effectiveness of the drug(s) you sell. GVP provides confidence that you have conducted pharmacovigilance activities in a consistent, reliable, and verifiable manner.

Please note that this guidance document does not cover all the legislation related to post-market pharmacovigilance and safety activities and/or amendments under the [Protecting Canadians from Unsafe Drugs Act \(Vanessa's Law\)](#) such as the [Food and Drugs Act](#) (act) sections 9, 21.1, 21.2, 21.31, 21.32, and the [regulations](#) C.01.003, C.01.004, C.01.013, C.01.014.1, C.01.052, C.01.053.

1.2 Scope

This guide applies to all persons (individuals and companies) involved in the post-market pharmacovigilance activities for the following 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.

This guide does 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.

1.3 Introduction

Guidance documents like this one are meant to help you understand how to comply with regulations for the purpose of GVP inspections. They also provide guidance to our staff, so that the rules are enforced in a fair, consistent and effective way across Canada.

We inspect manufacturers to assess compliance with the [act](#) and associated [regulations](#). When we conduct an inspection, we will use this document as a guide in assessing your compliance with GVP requirements.

To better understand how risk ratings are assigned during inspections, see Risk Classification of Good Pharmacovigilance Practices (GVP) Observations (GUI-0063).

94 These guidelines are not the only way GVP regulations can be interpreted and are not
95 intended to cover every possible case. We may revise this guidance and adapt our policy
96 approach as new technologies emerge and mature, and as regulatory oversight optimizes.

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2.1 Guiding principles

You are responsible for meeting the requirements outlined in the act and regulations and clarified in our guidance documents. You will also need the help and commitment of your partners and personnel at all levels.

To meet these requirements, you need a robust pharmacovigilance system as it forms an integral part of Good Pharmacovigilance Practices.

With a robust system, you can:

- monitor the safety and effectiveness of your drugs
- notify Health Canada within the required timelines
- take reliable and timely actions based on the available evidence

To build a robust pharmacovigilance system, you should:

- set out a decision-making process with deliverables for consistency in all activities
- assign personnel who perform or oversee the deliverables
- ensure that responsibilities are well understood by internal and external parties
- ensure that enough qualified and trained personnel are available
- identify and evaluate performance indicators
- address any deficiencies in a timely manner

- carry out and monitor corrective and risk mitigation measures, as necessary
- document all activities to demonstrate that you met the deliverables

2.2 Written procedures

2.2.1 Overall considerations

You should prepare and document written procedures outlining pharmacovigilance processes with step-by-step instructions for relevant personnel and departments. These procedures should have unique identifiers.

Periodic reviews, as per established timelines, ensure that the written procedures continue to adhere to current expectations and accurately reflect current practices. The revision history, reason(s) for revision, revision number, and effective dates for written procedures should be documented accordingly.

Designated personnel should date, approve, and sign any revisions to the procedures (Refer to the [Personnel and training](#) section). All personnel and departments involved in pharmacovigilance should know when a procedure is revised and be trained before a revised procedure takes effect.

When pharmacovigilance activities are contracted to a third-party, you must ensure that roles and responsibilities, as well as step-by-step instructions are clearly documented in written procedures or contractual agreements. They should be easy to follow to allow contractors to comply with the applicable regulatory requirements (Refer to the [Contractual agreements](#) section.) Copies of procedures belonging to a third-party and contractual agreements should be made available during inspections.

Documentations should show that the procedures have been put into practice.

2.2.2 Deviations

A deviation is a change or departure from the steps and/or instructions outlined in an approved written procedure. These can be planned or unplanned.

In a planned deviation, the departure should be documented, evaluated and approved before the change is implemented.

In an unplanned deviation, the departure is unexpected and could suggest a systematic deficiency which needs to be resolved.

A systematic deficiency is a fundamental inadequacy that exists within the processes or mechanisms of a pharmacovigilance system. It can arise from inadequate planning, design, or oversight of the system. This deficiency impacts the system's ability to function effectively, consistently, and achieve its intended goal. It is widespread instead of isolated. A widespread incident is one that is part of a series or pattern of similar occurrences.

When there is an unplanned deviation, you should:

- document the deviation in a timely manner
- carry out an investigation
- evaluate if there is a systematic deficiency
- perform a root cause analysis to assess the cause and impact
- identify and carry out an effective corrective and preventative action plan (CAPA)
- evaluate if the corrective and preventative actions taken addressed the root cause of the deviation

Good quality control practices should be in place to detect deviations. You may periodically perform:

- data quality checks
- trend analysis of metrics

Periodic review of trends, performance, and processes will inform continual process improvements that are necessary to enable compliance and maintain a state of control.

2.2.3 Change control

Establish a change control system to allow ongoing process optimization and a continuing state of control. The quality control department must document, evaluate and approve all changes, as well as identify the appropriate effective date. Any significant change may require re-validation or verification of systems or processes.

2.3 Business continuity plan

2.3.1 Overall considerations

You should establish a business continuity plan, which can be implemented to enable you to continue critical operations during scenarios such as:

- periods of absence from regular business hours
- unexpected situations, such as:
 - an information technology breach
 - a network or system failure
 - catastrophic accidents
 - a pandemic
 - a sudden influx of litigation cases
- transition periods such as merging or migrating of pharmacovigilance databases

2.3.2 Merging or migrating databases

When merging or migrating pharmacovigilance databases, you should consider the following:

- principles on [record retention](#), [data integrity](#), and maintain an audit trail throughout the whole process, from beginning to end
- principles on [validation of computerized systems](#)
- Conduct an impact assessment to:
 - identify vulnerable areas of the pharmacovigilance system that may require testing, validation or re-validation, as well as assess the change or compatibility of data format
 - ensure merged or migrated data are stored properly
- Develop a risk mitigation strategy to ensure that original data is not lost or altered

2.4 Self-inspections

Self-inspections help you monitor your organization's compliance, including the compliance of third-parties. Your contractual agreement should outline your right to conduct periodic inspections on third-parties and should document the frequencies of these inspections.

2.4.1 Scope

The scope of your self-inspection program should cover all departments or third-parties that take part in your pharmacovigilance activities, for example, those that:

- receive, handle, document, process, evaluate, and submit [adverse drug reactions \(ADRs\)](#) and [unusual failure in efficacy \(UFIE\)](#) data
- conduct [environmental scanning](#) such as literature searches and regulatory authority database searches
- [manage signals](#)
- prepare, review, approve and submit notifications, [annual summary reports \(ASRs\)](#), and [issue-related summary reports \(IRSRs\)](#)
- monitor and notify us of [foreign actions](#) related to serious risk of injury
- implement risk mitigation actions

2.4.2 Overall considerations

Your self-inspection program should include:

- a comprehensive written procedure that describes the functions of your self-inspection program and must address all areas of the applicable regulations
- the need for responsible personnel who are independent from the pharmacovigilance department or third-parties, trained on Canadian GVP requirements, and are qualified to conduct the inspection
- the frequency of self-inspection activities based on a documented risk-based strategy
- prioritization of key processes that impact compliance with the regulations
- documentation and investigation of the root cause and impact when there is a [deviation](#)

- a review of any self-inspection findings by senior management, with an appropriate implementation timeline for each CAPA
- follow-up to ensure that all CAPA are completed in an appropriate time

2.5 Validation of computerized systems

Any electronic system used to capture, process, manage or archive pharmacovigilance activities should be validated based on how the system will be used. Validation confirms that the system is reliable, credible and will perform as expected. You should document how validation, testing, and re-validation is to be conducted.

Validation reports should be produced to document the results of the validation tests you performed. The results should clearly indicate that the system can be used as intended and is performing as specified.

Modifications or additions made to the electronic system, such as software upgrades or data migration, can affect performance. These can, in turn, affect the quality of the validated applications, and thus the integrity of electronic information. The system's reliability can also be questioned.

For these reasons, you should assess and approve all changes, using your change control system, to hardware or software used in pharmacovigilance activities. This assessment will also help determine if re-validation is needed and the scope of re-validation.

When conducting a risk-assessment regarding the validation of a computerized system, including when there is a change to the system, ask yourself the following questions such as:

- What is the purpose of the system (for example, to receive an ADR, to transfer or gather data)?
- What is the direct or indirect impact on the regulatory obligation? For example:
 - changes to reporting rules that impact ADR submissions
 - workflow status of a case that would affect the scheduling for electronic reporting
 - quality of data that may affect the monitoring of the benefit-risk profile of the drug

2.6 Personnel and training

2.6.1 Overall considerations

Employees, in-house or contracted, involved in pharmacovigilance activities must be adequately qualified and trained on the Canadian GVP requirements and their specific responsibilities. This applies to employees such as those who:

- conduct pharmacovigilance activities
- may receive [ADR/UFIE](#), such as:
 - sales or as customer service representatives
 - receptionists

- medical science liaison staff
- medical information officers
- handle [label update](#) such as the regulatory affairs department
- handle inspections such as the quality control department

Qualified alternate(s) should be identified to carry out duties when responsible personnel is/are absent.

You should ensure that employees:

- receive the level of training that aligns with their title and responsibilities
- receive continuous training relevant to their title and responsibilities
- have the practical experiences that align with their title and responsibilities

You should maintain records for in-house and contracted personnel such as:

- organizational charts
- proof of qualifications
- written work description with specific duties
- training records

2.6.2 Designated person to oversee pharmacovigilance activities

In addition to the above overall considerations, there should be a person designated to oversee pharmacovigilance activities to ensure that all requirements are met. An alternate with the required experience should be identified.

2.6.3 Qualified healthcare professional

The qualified healthcare professional (QHCP) is:

- a medically-qualified person such as a physician, dentist, pharmacist, nurse, coroner, or as otherwise specified by local regulations
- who is entitled to provide healthcare under the laws of the jurisdiction in which the person is located

Note: A qualified health professional can also be an individual with the appropriate healthcare education and therapeutic expertise, employed by you.

This individual should be involved in key pharmacovigilance activities such as:

- evaluating whether the new information based on [follow-up](#) efforts is considered clinically or medically significant/relevant that requires expedited reporting
- verifying [coding](#) selection of complex/less intuitive ADRs based on MedDRA (Medical Dictionary for Regulatory Activities)
- providing medical knowledge on [evaluations](#) or changes to evaluations related to the seriousness, expectedness, and causality of ADRs, as well as assessments on UFIE

- reviewing and approving [annual summary reports \(ASRs\)](#) and [issue-related summary reports \(IRSRs\)](#)
- providing clinical or medical judgments on [signal management activities](#), as well as any follow-up actions or risk mitigation strategies
- determining if a product is implicated by a [foreign action](#) and the extent of similar ingredients applicable to your search on foreign actions

2.7 Contractual agreements

2.7.1 Delegation of pharmacovigilance activities

You may delegate a pharmacovigilance activity to a third-party or contractor. However, if you do, **you continue to be ultimately responsible for meeting all regulatory requirements and principles of GVP described in this guidance document. You must ensure processes are in place to control outsourced activities.**

You should have a written agreement that is signed and dated between your organization and the third-party.

At minimum, a contractual agreement should exist between the MAH and the following parties:

- global entities under the same ownership or corporate structure
 - unless processes are already outlined in corporate procedures
- service providers or external parties outsourced to conduct the following pharmacovigilance activities on your behalf such as:
 - receive ADRs
 - manage PSPs
 - perform literature searches
 - execute terms and conditions
 - post-marketing studies
- companies whose names or contact information is/are included in the physical or electronic product label or electronic platforms such as third-party private labelers

2.7.2 Elements of a contractual agreement

Your contractual agreement should include the following, at minimum:

- roles and responsibilities of each party for each specific activity
- effective date of the agreement
- a list of products that are in scope
- definition of all relevant pharmacovigilance terms
- timeline and scope of safety information to be exchanged
- dated signature of the relevant officials from both parties
- contact information of both parties

Your contractual agreement should also require:

- that there be no subcontracting of any work without written authorization from you
- a reconciliation process for pharmacovigilance data, outlining the methodology and frequency, to ensure that any missed communication about ADR reports or signals are addressed in a timely manner
- any changes to the pharmacovigilance system(s) be governed by a change control system
- both parties be notified of any changes to the pharmacovigilance system when an in-scope product is impacted
- the third-party to provide all records related to the outsourced activities to you in a timely manner when requested
- the third-party to assist in inspections conducted by you and inspections conducted by regulatory authorities (such as by providing relevant records and attending interviews)
- any potential impacts on pharmacovigilance activities be communicated between you and the third-party

The agreement should be reviewed periodically to reflect current requirements and practices.

You must provide the contractor with all the information needed to carry out contracted operations correctly, according to all legal requirements.

2.7.3 Cross-licensed product

You are responsible for pharmacovigilance responsibilities on the DIN that you own. When your drug is a cross-licensed product, your contractual agreement should ensure that proper communication takes place to enable you and your cross-licensed partner (between the licensor and licensee) to individually fulfil your responsibilities. For example:

- the licensor and licensee should take proactive efforts to [update the product label](#) or monograph as necessary
- the licensor should take proactive efforts to communicate with the licensee about any [safety signals](#) and considerations on [risk mitigation strategies](#)
- the licensee should take proactive efforts to communicate with the licensor about any [safety signals](#) and considerations on [risk mitigation strategies](#)

2.7.4 Merger and acquisition

Compliance with requirements set out in the regulations and the GVP principles in this guidance document must continue during transition periods such as a merger, acquisition, or migration of pharmacovigilance databases. A contractual agreement should be in place to outline roles and responsibilities in order to ensure compliance. You must minimize any impact on ongoing pharmacovigilance activities.

Please refer to the [Business continuity plan](#), [Validation of computerized systems](#), and [Maintenance of records](#) sections for further information regarding expectations during transition periods.

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- 3.8 [Unusual failure in efficacy](#)
- 3.9 [Label update](#)

For each section below, the exact text from the regulations are provided first. This is followed by the rationale (why the rule is important) and our interpretation (what you should do to be compliant), where needed.

To sell a drug, you must comply with the regulations and apply Good Pharmacovigilance Practices (GVP) as described in this guidance. As a manufacturer or MAH, you must ensure that your products are safe and effective throughout their lifecycle.

The [act](#) defines “sell” as:

- offer for sale, expose for sale or have in possession for sale, or distribute to one or more persons, whether or not the distribution is made for consideration, and
- lease, offer for lease, expose for lease or have in possession for lease

Note: The responsibility to comply with C.01.014.21 of the regulation starts as soon as a term and condition is imposed on your Drug Identification Number (DIN).

Note: The responsibility to comply with C.01.050 of the regulation starts once you receive a DIN (subsection C.01.014.2(1)) or a Notice of Compliance (NOC) (section C.08.004 or C.08.004.01).

3.1 Terms and conditions

C.01.014.21 of the regulations

C.01.014.21

(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)

Note: As part of the amendment of certain regulations (Agile Licensing) under the act, there are proposed legislative changes that will allow for the future application of terms and conditions to a broader scope of DINs. Refer to [Regulations Amending Certain Regulations Made Under the Food and Drugs Act \(Agile Licensing\): SOR/2024-238](#) for more information.

Rationale

Terms and conditions (T&Cs) are a regulatory tool that can be applied for additional oversight on the safety, efficacy, and quality of an authorized drug throughout its life cycle. The main objective of imposing T&Cs is to ensure that a drug retains the favourable benefit-risk profile demonstrated at the time of market authorization.

Interpretation

This section should be read along with the following guidance documents. You are expected to fulfill all the requirements outlined within:

- [Submission of targeted risk management plans and follow-up commitments for prescription opioid-containing products – Guidance for industry](#)
- [Guidance on the Food and Drug Regulations for public health emergency drugs](#)
- [Submitting risk management plans guidance document](#)

A new T&C may be imposed on a drug identification number (DIN) or the existing T&Cs on a DIN may be amended at any time. You, as the MAH/manufacturer must comply with them.

T&Cs vary depending on the product and can include pharmacovigilance and risk minimization activities/measures.

You should have a system and process in place to execute the activities/measures outlined in the T&Cs in a timely manner or within the specified timelines. All elements of a pharmacovigilance system should be applied. You should also monitor the progress on these activities and resolve any challenges to ensure proper execution of the T&Cs.

3.2 Prohibition

C.01.016 of the regulations

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.

3.3 Serious adverse drug reaction reporting

C.01.017 of the regulations

C.01.017

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

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

Rationale

As the manufacturer, you must collect, evaluate, and submit adverse drug reactions (ADRs) in a timely manner. This allows you to monitor the safety and effectiveness of drugs being sold and submit ADR information to us accordingly.

Interpretation

This section should be read along with the following guidance document. You are expected to fulfill all the requirements outlined within:

- Reporting adverse reactions to marketed health products – Guidance document for industry

Overall considerations

You should have approved [written procedures](#) and instructions for receiving, handling, documenting, processing, evaluating, and submitting ADR. All elements of a pharmacovigilance system should be applied. Documented information on domestic and foreign ADRs should be accurate, complete, and consistent. You must submit this information to us within 15 calendar days of receiving a report, if the Individual Case Safety Report (ICSR) qualifies for 15 calendar days expedited reporting.

Receiving, handling, documenting, and processing ADR data:

Overview

An Adverse Event (AE)/ADR may be received from internal departments or external third parties delegated to act on your behalf. These include, for example:

- entities that conduct patient support programs (PSP)
- entities to conduct post-marketing activities such as studies or literature search
- international entities under the same ownership or corporate structure or entities on the product label
- the entity that handles customer service or marketing activities that are owned, controlled, or operated by you

You should ensure your systems and procedures:

- define the terms used in pharmacovigilance activities
 - for example, ADRs and serious ADRs
- enable the receipt and handling of incoming correspondences that represent potential domestic and foreign ADRs

- transfer any AEs/ADRs received to the pharmacovigilance department
- identify the responsible personnel or contact person who receives incoming correspondences from the contact point identified on the product label or any advertising material and digital platform
- assign a unique identifier to each incoming case
- define day zero (day 0) as the day when all 4 minimum criteria of the ICSR are available to you or the party delegated to conduct pharmacovigilance activities on your behalf (refer to the definition on day 0 in the [Glossary](#))
- define the process to validate and invalidate ICSRs
 - The record of invalidated cases should be maintained for inspection purposes
- define timelines and workflow for triaging safety information to the pharmacovigilance department for processing
- define the process for after-hours operations
 - for example, timeline for handling incoming voice messages and incoming text messages via chat bots or other electronic platforms
- track all programs or studies managed by third-parties or other departments that may receive AE/ADR reports
 - refer to the [Contractual agreements](#) section for expectations when you delegate pharmacovigilance responsibilities to third-parties
- clarify who is responsible and the process for translating AE/ADR correspondence into English or French, when necessary

To ensure completeness of ADR information, you should exercise due diligence in seeking and recording information of key data elements:

- obtain consent to [follow-up](#), document any follow-up attempts, and information obtained from follow-up
- query the reporter to obtain the most complete information possible, while ensuring to avoid inferences and imputations.
- retain a consumer's description of the event, but also seek confirmatory or additional information from relevant healthcare professionals who are directly involved in the patient's care
- include the verbatim term used by the reporter, or an accurate translation if provided in a language other than English or French
- provide an unbiased and unfiltered report of information received

Note: Please refer to the [Environmental scanning](#) section for guidance on conducting literature searches. While reviewing the scientific literature, you may become aware of ICSRs qualifying for expedited reporting under C.01.017 of the regulations.

Note: Compulsory licence holders of Canada's Access Medicines Regime (CAMR) are subject to the requirements for reporting foreign ADRs on drugs sold under [CAMR](#).

Coding

To promote accurate and consistent term selection when different options are possible, you should use recommendations detailed in the [MedDRA® Term Selection: Points to consider](#) document.

Your approved procedures and instructions should ensure that:

- AE/ADR terms are coded consistently
 - any inconsistencies should be justified and documented by the [Qualified Healthcare Professional \(QHCP\)](#)
- the coding reflects up-to-date MedDRA terminology, conventions and exceptions
 - [MedDRA: Support documentation](#)
- a risk-based strategy is identified that requires the [QHCP](#) to verify the coding selection of complex or less-intuitive AEs/ADRs
- the MedDRA version update process is outlined and that any impact analysis and risk-based review will be conducted when an update is made

Duplicates

Your approved procedures and instructions should describe:

- the strategy or algorithm in place to find ICSRs that are similar
- the verification process when potential duplicates in your pharmacovigilance database are identified
- how to manage duplicates in the database once validated
- how effective the strategies or algorithms are and fine-tune them over time as necessary

If you identify duplicates within your database after the reports have been submitted to us, you should inform the [Canada Vigilance Program](#).

For more information, consult:

- Reporting adverse reactions to marketed health products – Guidance document for Industry

The above-mentioned principles are important for proper [ADR evaluations](#), [ADR submissions](#), [Annual Summary Report \(ASR\) preparation](#) and [Issue-Related Summary Report \(IRSR\) preparation](#).

Following up with the reporter or patient:

You should have approved procedures and instructions for following up with the reporter or patient. For example, you should:

- seek the reporter's or patient's consent to follow-up

- reference the initial report in your follow-up submission to the Canada Vigilance Program
 - update corresponding data fields
 - identify new information and date of receiving follow-up information
 - ensure that the date when you received follow-up information does not precede the latest date of previous report versions
- follow-up to identify missing information that allows meaningful case evaluation:
 - 4 minimum criteria of the ICSR
 - key data elements
 - for example, patient and reporter identifiability is important to avoid case duplication, ensure authenticity, and facilitate follow-up
 - verify duplicate information and resolve any information that conflicts with the original information that was collected
- document all follow-up efforts to show diligence and optimization to collect missing information
 - document decisions and justifications to either not follow-up or to discontinue follow-up efforts
- involve [QHCPs](#) with the appropriate level of pharmacovigilance training and therapeutic expertise in the collection of information and direct follow-up of reported cases, when possible
- document information received from follow-up systematically
- prioritize the different types of case reports for follow-up considering the seriousness and expectedness, as well as case reports of special interest
 - Note: Although some of these cases may not be subject to expedited reporting, you should still pursue follow-up on these reports.
- have a risk-appropriate strategy that references the QHCP's judgment, to determine the amount of time devoted to follow-up
- follow-up should always be conducted on observations without an AE/ADR such as overdose, abuse, misuse, medication error, occupational exposure, pregnancy or lactation exposure to ensure that information is as complete as possible with regard to the suspected product and the context of occurrence

Note: When additional clinically or medically significant/relevant information is received from an ICSR previously submitted to the Canada Vigilance Program, the regulatory reporting time clock of this follow-up information begins again. You must report it within 15 calendar days of receipt.

Clinically or medically significant/relevant follow-up information relates to, for example:

- new or changed suspected adverse reaction(s)
- additional or changed suspect product(s)
- a change in the causality assessment
- any new or updated information about the case that affects the product's medical interpretation

You must seek the clinical or medical judgment of a [QHCP](#) on significant/relevant new information that requires expedited reporting.

The above-mentioned principles are important for proper [ADR evaluations](#), [ADR submissions](#), [ASR](#) preparation and [IRSR](#) preparation.

Evaluating ADR reports:

You should have approved procedures and instructions for evaluating AE/ADR reports you received and retrieved. For your AE/ADR report, you should:

- assess seriousness consistently for a given ADR
 - consider how serious ADRs are defined in the regulations and based on the ICH official definition of seriousness
 - consider medically important events consistently when assessing “seriousness”
- determine the expectedness for both domestic and foreign AE/ADR reports from the current product monograph, labelling standards, information approved for market authorization, or product label
- verify if an AE/ADR report is solicited or spontaneous
 - if solicited, you must assess causality before submitting to us. In addition, you must respect the opinion or causality assessment of the reporter, that is, not downgrade the report even if you disagree with the reporter.
 - if spontaneous, ADR reports have implied causality. As such, your causality assessment will not affect whether the report should be submitted to us.
- record the opinions or assessment of both the reporter and you in the narrative section of the report if there is disagreement about the seriousness or causal relationship between the suspected product and the reported AE/ADR
- evaluate and document the assessment if follow-up information changes the seriousness, expectedness and/or causality assessment
- evaluate if follow-up yields clinically or medically significant/relevant information that prompts the need to submit a report to us
- justify the evaluation of an AE/ADR and document the [QHCP’s](#) medical assessment

For more information, consult:

- Reporting adverse reactions to marketed health products – Guidance Document for Industry

Submitting ICSRs to us:

You should have approved procedures and instructions for submitting an ICSR. For example, you should:

- require that domestic serious ADRs and foreign serious unexpected ADRs be submitted to us within 15 calendar days of receiving or becoming aware of the adverse drug reaction (refer to the day 0 definition in the [Glossary](#))
- complete all the processes (triage, transfer of safety information, processing, documentation, evaluation) in time to meet the 15 calendar days timeline of submission after receiving or becoming aware of the ADR

- verify that your reporting rules meet the Canadian reporting requirements if you use an electronic pharmacovigilance system
- submit clinically or medically significant/relevant follow-up information related to a previously submitted ADR report to us within 15 calendar days of receiving such follow-up information
- Nullification requests can be requested on ICSRs previously submitted to the Canada Vigilance database only if further information confirms that the case is a duplicate or the case was found to be erroneous
 - Furthermore:
 - The record of nullification and associated documents should be maintained.
 - Documented procedure and process should be in place describing when ADR reports may be nullified.
 - A nullified case is one that should no longer be considered for scientific evaluation.

Note: Post-authorization safety studies with secondary data are not subject to expedited reporting to us. However, these case reports are expected to be included in [ASRs](#).

3.4 Annual summary reports and case reports

C.01.018 of the regulations

C.01.018

- (1) The manufacturer shall prepare an annual summary report of all information relating to adverse drug reactions and serious adverse drug reactions to the drug that it received or became aware of during the previous 12 months.
- (2) The annual summary report shall contain a concise, critical analysis of the adverse drug reactions and serious adverse drug reactions to the drug.
- (3) In preparing the annual summary report, the manufacturer shall determine, on the basis of the analysis referred to in subsection (2), whether there has been a significant change in what is known about the risks and benefits of the drug during the period covered by the report and shall include its conclusions in this regard in the summary report.
- (4) If, in preparing the annual summary report, the manufacturer concludes that there has been a significant change, it shall notify the Minister without delay, in writing, unless this has already been done.
- (5) The Minister may, for the purposes of assessing the safety and effectiveness of the drug, request in writing that the manufacturer submit to the Minister one or both of the following:
 - (a) the annual summary reports
 - (b) the case reports relating to the adverse drug reactions and serious adverse drug reactions to the drug that are known to the manufacturer.
- (6) The Minister shall, after giving the manufacturer an opportunity to be heard, specify a period for the submission of the annual summary reports or case reports, or both, that is reasonable in the circumstances, and the manufacturer shall submit the reports within that period.

Rationale

The preparation of an annual summary report (ASR) is a tool which summarizes interval safety data and allows the manufacturer to conduct an overall safety evaluation. The ASR can be used to identify safety signals or changes to what is known about the risks and benefits of the drug.

Interpretation

This section should be read with the following guidance documents. You are expected to fulfill all the requirements within:

- Guidance on preparing and submitting summary reports for marketed drugs and natural health products

Preparing ASRs

The ASR should provide a concise and critical analysis of interval safety data. The preparation of an ASR is an ongoing activity throughout the reporting period linked to signal management processes and monitoring activities. Continuous and periodic signal management processes and monitoring activities, such as environmental scanning, are important for the preparation of an ASR. As the manufacturer, you should conduct regular, systematic analyses of safety data to identify new or emerging information on a drug's benefits and risks.

A significant change in what is known about the risks and benefits of a drug can occur at any time during the preparation of the ASR, depending on the available evidence. The ASR does not need to be complete for you to conclude that there has been a significant change. If there is a significant change in what is known about a drug's risks and benefits, you must notify us without delay.

Refer to the Guidance on preparing and submitting summary reports for marketed drugs and natural health products for the definition of significant change and to obtain information on what to include in the notification to us.

You should have a [system](#) including approved procedures and instructions. All elements of a pharmacovigilance system should be applied. Your system should enable you to:

- prepare, review, and approve ASRs in a timely manner
 - have the [qualified healthcare professional \(QHCP\)](#) review and approve the ASR
 - include all the sections and information expected by ICH E2C (R2) periodic benefit-risk evaluation report (PBRER), ICH E2C (R1) periodic safety update report (PSUR), or non-standardized format and as explained in Guidance on preparing and submitting summary reports for marketed drugs and natural health products

- apply consistent processes when preparing ASRs such that each annual assessment illustrates trends from 1 year to another (justify, document, and indicate the impact when the process has changed)
- conduct signal management and environmental scanning as part of the ASR preparation
- Note: Post-authorization safety studies with secondary data do not require expedited reporting to us. However, these case reports are expected to be included in ASRs.
- assess and notify us on significant change in a timely manner
- submit ASR and case reports if being requested

Signal management

As part of ASR preparation, continuous and periodic signal management processes are needed. Signals that meet the definition of a significant change should be reported to us without delay.

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).

As part of preparing the ASR, you should have a [written procedure](#) for your signal management practices.

Overall considerations

You should ensure that:

- your system allows a consistent approach in the signal management process such as the detection and evaluation of signals
- the pharmacovigilance department meets regularly to review and discuss safety signals
- [QHCPs](#) with the relevant area of expertise are involved in the signal management process
- the status of each safety signal are tracked, including at minimum:
 - its assessment or justification,
 - follow-up actions such as necessary updates to the product label or Canadian Risk Management Plan (RMP) and its proposed timelines,
 - any significant change in what is known about the risks and benefits of the drug
- signal management is performed in a timely manner
- if it applies to a [cross-licensed product](#), have a [contractual agreement](#) in place between the licensor and licensee describing 2-way responsibilities for the exchange and assessment of safety information

- case reports and any information related to the signal management process are kept for 25 years from when they are created as per [C.01.020](#) of the regulations

Signal detection:

You should:

- conduct signal detection on an ongoing basis
 - the timing, frequency, and nature of monitoring activities depend on several factors, such as:
 - the drug's risk and uncertainty profile
 - known or specific emerging issues
 - scheduled timing or preparation of the ASR
 - volume of ADRs received
 - justify and document the decision that the agreed upon periodicity to conduct signal detection is sufficient
 - the timing of environmental scanning, such as searches on regulatory authority databases, should align with the timing of data updates from these databases
- ensure that all report types being accounted for in the ASR of a product are consistently used across all reporting intervals
- identify search criteria used in signal detection
 - justify and document the search criteria such as MedDRA terms, MedDRA version, and level of MedDRA hierarchy used, as applicable
 - justify changes made to the search strategy
 - demonstrate the data retrieved using the previous and new search terms are comparable (note any differences and document impact analysis)
- describe the qualitative and quantitative methods used to detect signals
 - use them consistently across different reporting intervals and justify changes where applicable
 - document medical assessment and statistical considerations to identify an appropriate threshold

Signal evaluation:

You should:

- analyze available information in a timely manner, which could involve, for example:
 - causality analysis
 - utilization and exposure analysis
 - medical analysis
 - scientific analysis
 - assessment of previous actions taken
 - a review of Canadian and international perspectives and considerations
 - assessment of actions from other regulatory agencies
- date, sign, and document any justifications and decisions on signals such as those that are closed or ongoing

- document the timeline to resolve any ongoing signals, supported by risk-relevant information

Environmental scanning

To conduct a critical analysis of the ADRs and serious ADRs to the drug, continuous monitoring activities such as environmental scanning is needed. Environmental scanning may include literature searches, Canadian regulatory authority database searches, and foreign regulatory authority database searches. Please also refer to the [Foreign action section](#) for specific classes of products subject to C.01.050 of the regulations as this is part of environmental scanning.

Conduct a [literature search](#) for ADRs and safety concerns at least once every two weeks or provide a rationale to justify a reasonable search frequency (a similar process should be put in place to systematically retrieve ADRs and safety concerns from other sources of environmental scanning):

You should:

- establish a process to identify and document ADRs, indicate:
 - the search frequency
 - the search strategy such as terms, limits, and sources
 - how to determine if the literature is within scope of the drug in question
- identify Canadian and international literature sources relevant to the drug you sell, such as:
 - large reference databases
 - local Canadian scientific journals that are not indexed in worldwide databases
 - specialized publications
- keep the list of Canadian and international literature sources updated, adding relevant new journals as necessary
- identify and document the product search terms used for a search (including the medical justification), such as:
 - indexed terms
 - active ingredient
 - variations in spelling or names of the active ingredient if it is not indexed, such as:
 - chemical or brand names, active metabolites or names previously used in clinical trials
 - medically relevant variants or compounds of the active ingredient that would be considered the same drug
 - product brand name or alternate product names of the same drug sold by other manufacturers or MAHs locally and globally
 - class of drug
- consider post-authorization safety studies that use primary or secondary data
- account for safety findings in the relevant summary report, including ones that do not qualify for Individual Case Safety Report submission

- identify, assess, and document relevant safety information such as medication error, overdose, drug abuse, or misuse, even without ADRs
- always document the literature reference and verify if any [duplication](#) exists within your pharmacovigilance database
- retrieve the complete publication when the source article was cited as a reference in a publication during literature search
- consider the same combination of active ingredients even if the formulation, dosage form, strength, route of administration or indication vary
- document the medical reason for using search terms related to risks
 - accounting for terms such as “risks under active surveillance” that regulatory authorities may have requested
- consider how updated sources or those that are added later will be retrieved, and the limits that will be applied to a search, for example:
 - date ranges that conform to the publishing schedule
 - date ranges should consider records that may be added later in the day of the day of the search
- keep records of literature searches, including records of:
 - search strategies
 - sources or databases searched
 - search results for a given date range, even when the search did not yield any results
 - important decisions made during the literature search

Actions taken based on your analysis for safety reasons:

Your ASR should address and assess the need for actions taken for safety reasons such as changes to the product label or the introduction of/update to the Canadian RMP and summarize changes as appropriate.

If no follow-up actions are necessary, you should document your justification.

You should continuously evaluate whether any revision of the product label is needed when new safety information arises such that ASRs are prepared based on the latest information on the label. Refer to the [Label update](#) section for more information.

The proposal to update label or introduce or update the RMP should be included in the ASR. Your system and processes should allow implementation of these proposals. In the event where the RMP or element(s) of the RMP is a T&C applied on your DIN, refer to the [Terms and conditions](#) section for more information.

Note: If there is a significant change on what is known about the risks and benefits of the drug, you should notify us without delay. Refer to Guidance on preparing and submitting summary reports for marketed drugs and natural health products on notifications to us.

3.5 Issue-related summary reports

C.01.019 of the 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 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.

Rationale

The issue-related summary report (IRSR) is a practical tool that summarizes a specific issue regarding a drug, at the request of the Minister, for the purposes of assessing its safety and effectiveness.

Interpretation

This section should be read with the following guidance documents. You are expected to fulfill all the requirements outlined within:

- Guidance on preparing and submitting summary reports for marketed drugs and natural health products

As the manufacturer, you should have a [system](#) including approved procedures and instructions to prepare, review, approve and submit an IRSR. All elements of a pharmacovigilance system should be applied.

You should:

- provide the IRSR within the timeframe specified by the Minister
- ensure the pharmacovigilance department has mechanisms in place, within its own department or in collaboration with relevant departments, so that IRSR requests are received, triaged to the appropriate department, prepared and reviewed by responsible personnel, and submitted to us by the specified timeline
- follow the search strategy specified in the IRSR request to retrieve cases

- document discussions with us if the search strategy was revised to retrieve a more comprehensive set of safety data
- document the rationale of the search strategy (such as the particular MedDRA level and search terms being included) if not already specified by the IRSR request
- verify that all the relevant data are provided as per the IRSR request
- justify and document if aspects of the requested safety issue have been excluded
- ensure the data used in the IRSR analysis are complete and accurate
- maintain and make available upon request the IRSR and all data used to compile the report
- have a [Qualified Healthcare Professional \(QHCP\)](#) review and approve the IRSR
- follow record retention principles as per section [C.01.020](#) of the regulations to safeguard the integrity of the historical data
- refer to the [signal management](#) and [environmental scanning](#) sections for more information

3.6 Maintenance of records

C.01.020 of the regulations

C.01.020

- (1) The manufacturer shall maintain records of the reports and case reports referred to in sections C.01.017 to C.01.019.
- (2) The manufacturer shall retain the records for 25 years after the day on which they were created.

Rationale

Good documentation is an essential part of the pharmacovigilance system and promotes compliance with Good Pharmacovigilance Practices (GVP) requirements regarding record maintenance and retention. A good data governance system helps you, as the manufacturer, establish, control, monitor and record all activities that directly and indirectly impact the safety of drugs.

Interpretation

Overview

Documentation may be paper-based and/or in electronic form. The various types of documents and different forms of documentation used should be fully defined through [written procedures](#) of the [pharmacovigilance system](#).

As the manufacturer, you are responsible for maintaining and retaining records related to sections C.01.017-C.01.019 of the regulation for 25 years, regardless of the form of documentation (paper records or electronic records). This responsibility applies to you even when a pharmacovigilance activity is delegated to a third-party vendor. You should

have approved and up-to-date procedures and instructions for record maintenance and retention.

Record retention involves:

- keeping applicable records for at least 25 years after they were created, including at minimum:
 - all records, including source documents, follow-up, evaluations, submissions, of [adverse drug reactions \(ADRs\)](#)/case reports/[unusual failure in efficacy \(UFIE\)](#)
 - [Annual summary reports \(ASRs\)](#), the data used, and related communications with us
 - [Issue-related summary reports \(IRSRs\)](#), the data used, and related communications with us
- accessing records within a reasonable timeframe during the retention period
- providing documentation requested for evaluation by us in 1 of the official languages
- outlining the procedure used to maintain ADR records, including the filing system or electronic database used to retrieve these records
- ensuring the data is secured by physical or electronic means against willful or accidental damage or loss
 - refer to the [Data integrity](#), [Business continuity plan](#) and [Validation of automated computerized systems](#) sections for principles related to records maintenance and retention
- data back up at regular and predefined intervals to protect against potential data loss due to system issues or data corruption or unexpected events
- documenting that the [QHCP](#) was involved in key pharmacovigilance activities through:
 - physical or electronic initials or signatures
 - time stamp of the activity conducted by the QHCP
 - audit trail and change history as applicable
 - record of justification by the QHCP

Data integrity

You are responsible for establishing a data governance system that ensures the integrity of the retained data. You should:

- ensure that documentation is reliable, complete, consistent and accurate
- ensure controls are in place to prevent and detect data integrity issues throughout the product's lifecycle, for example:
 - have procedures that outline management's expectations for how data should be acquired, modified, reviewed and stored
 - when applicable, having [validated computer systems](#)
- apply the general principles of good documentation practices to all records, including those that are modified
 - having the ability to trace records to their source through:
 - initials and signatures

- secure user identification
- change history and audit trails that capture relevant information, such as the assessment or any change on seriousness, expectedness, causality and other entries such as date of receipt
- having legible records, with no parts of the data obscured or removed. If archived, they must be retrievable in a timely way. Any changes to records must also be documented and traceable
- ensuring that data are recorded, documented or saved when they're generated, with reliable evidence that this was done
- granting access to view, create, modify, and store data to authorized personnel only, to protect personal information, as well as ensure confidentiality and accuracy
- ensuring that records are kept in their original format as an original record or as a true copy which has undergone a qualified conversion process that maintains data integrity
- ensure that records are generated and maintained under the oversight of a pharmacovigilance system that ensures their accuracy
 - cloud computing servers are to be treated as a delegated service, with risks identified and addressed, and responsibilities clearly outlined in a [contractual agreement](#)

Additional considerations for electronic records

If you use an electronic system to create, modify or store records required under section C.01.020 of the regulation, you should [validate the system](#) for its intended use.

You should:

- control all access and user rights in electronic systems to prevent system users from compromising data integrity
- keep an up-to-date list of individuals who are authorized to access the system with defined user rights that support their roles and responsibilities
- control electronic records in a way that ensures the records:
 - can only be created and modified by authorized personnel
 - are protected against intentional or accidental deletion
 - are named and organized so they can be traced easily
 - are tracked through an audit trail, which should include:
 - changes made to the record
 - who made the change
 - the time and date the record was changed
 - the reason the record was changed, if applicable
 - are available for review during an inspection and can be easily retrieved in a suitable format
 - include all necessary metadata

An electronic signature is an acceptable alternative to a handwritten signature. Ensure appropriate controls are in place for electronic signatures, including:

- valid electronic signature systems to show that the systems are suitably secure and reliable
 - document this validation
- a procedure for creating electronic signatures, with controls in place to ensure each one is unique
- a time and date stamp (for audit trail requirements)

Inform users that electronic signatures are considered an equivalent to handwritten signatures. Keep records to show that users are aware of their responsibilities when using electronic signatures.

3.7 Foreign action related to serious risk of injury to human health

C.01.050 of the regulations

C.01.050

- (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.

Note: For the purpose of this guidance document, only foreign actions related to the safety of the drug will be reviewed during a Good Pharmacovigilance Practices (GVP) inspection.

Rationale

Many drugs may be marketed years in advance or in higher volume in other countries. For this reason, important safety signals are often detected earlier in a foreign jurisdiction. The foreign notification provisions make it possible for us to know early on about regulatory actions taken in a foreign jurisdiction.

Interpretation

This section should be read with the following guidance document. You are expected to fulfill all the requirements outlined within:

- Notifying Health Canada of foreign actions – Guidance Document for Industry

As the MAH who holds a Drug Identification Number (DIN) and Notice Of Compliance (NOC), you must provide us with information on foreign actions within 72 hours after you receive or become aware of the information, whichever occurs first.

As the responsibility to report foreign actions remains with the MAH, you must define roles and responsibilities with any global counterparts, affiliates, and any third-party vendors through procedures and contractual agreements. The established procedures and contractual agreements must facilitate timely exchange of information on foreign actions that promote compliance with regulatory reporting obligations.

In the situation where you, as the MAH, delegated the task to a global counterpart, affiliate, or contractual partner to monitor and identify foreign actions on your behalf, the 72-hour clock would start when these delegated parties become aware of such information.

In the situation where a global counterpart, affiliate, or contractual partner becomes aware of a foreign action but was not delegated specifically to identify foreign actions on your behalf, the 72-hour clock starts when you, the MAH, receive or become aware of such information.

You should have a [system](#) including approved procedures and/or contractual agreement for monitoring foreign actions.

Your procedures and/or [contractual agreements](#) should enable your organization to regularly monitor and identify information on foreign actions and provide this information to us in a timely manner. The procedure and/or contractual agreements should include information on, for example:

- roles and responsibilities to monitor, identify, and provide information to us
- how a serious risk of injury to human health is defined
- how often you conducted a search
- the search strategies you used to monitor and identify this information from each listed regulatory authority
- how to determine relevance to the safety of the drug you sell

You should also:

- consider how often and when you search an agency's website based on factors such as:
 - agency's publishing history
 - the product's risk profile
 - known or specific emerging issues
 - scheduling of Annual Summary Reports (ASRs)
- monitor information sources from the [List of Foreign Regulatory Authorities for the Purposes of Section C.01.050 of the Food and Drug Regulations](#)
 - Note: This applies to all the listed authorities regardless of who your market authorization is with.
- apply broad search strategies beyond merely searching by brand name or active ingredient
 - medical assessment by the [qualified healthcare professional \(QHCP\)](#) should determine if similar ingredients, molecules or class effect are relevant to the safety of the drug that you sell in Canada
- document and date search results
- assign personnel who will be responsible for identifying and assessing the foreign action, and for recommending actions to be taken in Canada
- document and date medical assessments performed by the [QHCP](#) on:
 - whether the serious risk of injury threshold has been met and
 - actions recommended in Canada
- have a manual review process, with established timelines for foreign regulatory authorities that do not have an automated alert system
- have a process for monitoring automated alert systems, to ensure they continue to function effectively and generate the intended results

- maintain notification records that have been submitted to us such as the automatic confirmation being issued

3.8 Unusual failure in efficacy

C.08.007 (1)(h) and 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.

Rationale

As a manufacturer, you must retain and submit records on Unusual Failure in Efficacy (UFIE) to monitor the safety and effectiveness of drugs being sold.

Interpretation

This section should be read along with the following guidance document. You are expected to fulfill all the requirements outlined within:

- Reporting adverse reactions to marketed health products – Guidance document for industry

Please refer to the Reporting adverse reactions to marketed health products – Guidance document for industry for the definition of UFIE.

As a manufacturer, you should have [systems](#) and procedures to report UFIEs to us within 15 calendar days of receiving such information on new drugs marketed in Canada. All elements of a pharmacovigilance system should be applied.

You should:

- follow the principles discussed in [section C.01.017](#) when receiving, handling, documenting, processing, following up, evaluating and submitting UFIE reports
- refer to [section C.01.020](#) regarding record maintenance and retention for unusual failure in efficacy reports as they are subject to [annual summary reports \(ASRs\)](#) and [issue-related summary reports \(IRSRs\)](#)

- have a [Qualified Healthcare Professional \(QHCP\)](#) evaluate and document failure in efficacy cases to determine if the case qualifies for expedited 15 calendar days reporting
 - clinical or medical judgment should be exercised
 - document and justify when a failure in efficacy report was not evaluated as unusual

3.9 Label update

C.08.003 of the regulations

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.

Note: For the purpose of this guidance document, only changes or processes related to the safety or efficacy of the drug will be reviewed during a Good Pharmacovigilance Practices (GVP) inspection. It is your responsibility to ensure compliance with other applicable regulatory requirements set out within the act and regulations for your products.

Rationale

Manufacturer with a new drug in which a notice of compliance has been issued, has the responsibility to file supplemental submission if current information is significantly different from information that supported your authorized product.

Interpretation

This section should be read along with the following guidance documents. You are expected to fulfill all the requirements outlined within:

- [Guidance Document: Product Monograph](#)

- [Guidance Document: Post-Notice of Compliance \(NOC\) Changes: Safety and Efficacy Document \(for pharmaceutical, biologic and radiopharmaceutical drugs for human use only\)](#)
- [Guidance document: Administrative processing of submissions and applications involving human or disinfectant drugs](#)

It is the manufacturer's responsibility to update product labels to be consistent with current scientific information and medical treatment.

If an update to the product label is warranted, you, as the manufacturer or MAH, should have a [system](#) and procedures in place to allow timely label update. All elements of a pharmacovigilance system should be applied. You should:

- establish a tracking system to monitor product safety updates that are pending, submitted, approved and implemented
- outline a risk-based process with your regulatory affairs department to ensure that product safety updates are communicated with us or submitted in a timely manner

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

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4 Glossary

Acronyms

ADR: adverse drug reaction
 AE: adverse event
 ASR: annual summary report
 DIN: Drug Identification Number
 ICH: International Council for Harmonisation
 ICSR: individual case safety report
 IRSR: issue-related summary report
 GVP: good pharmacovigilance practices
 MAH: market authorization holder
 NOC: notice of compliance
 ODCS: organized data collection system
 PSP: patient support program
 QHCP: qualified healthcare professional
 RMP: risk management plan
 T&C: terms and conditions
 UFIE: unusual failure in efficacy

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 [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. 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.

(adopted from 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)

Causality assessment:

The evaluation of the likelihood that a drug was the causative agent of an observed ADR in a specific individual. Causality assessment is usually made according to established algorithms.

Closed signal:

A signal for which an evaluation was completed during the reporting interval.

(ICH E2C (R2))

Cross-licensed product:

It is a drug product (for which a licensee is seeking market authorization) where all aspects of the submission or application are identical to that of the licensor in terms of all clinical data, chemistry and manufacturing data, product formulation, strength, route of administration, dosage form, authorized indication(s) and condition(s) of use as well as all product labels. For a cross-licensed product to be eligible for administrative processing the licensor's product must have received authorization from us; its DIN must not have a cancelled status at the time of the licensee's submission or application filing.

Data lock point:

The end date of a reporting interval as covered by the respective ASR. Also the cut-off date for data to be included in the ASR.

Day zero (Day 0):

The regulatory time clock for reporting ADRs or UFIE starts (day 0) on the date when any personnel of the manufacturer or the third party acting on their behalf has all the information satisfying the minimum criteria for constituting an Individual Case Safety Report (ICSR).

For follow-ups, day 0 is the day on which the manufacturer receives new clinically or medically significant/relevant information from a previously submitted case.

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)

Identified risk:

Untoward occurrences or undesirable clinical outcomes for which there is sufficient scientific evidence to show they are caused by the drug.

Individual case safety report (ICSR):

A description of an ADR in a single patient at a specific point of time. A valid ICSR must include these minimum criteria:

- at least one ADR
- an identifiable patient
- at least one suspect product
- at least one identifiable reporter

(adopted from ICH E2D (R1))

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.

Market research program:

Market research programs are ODCS which are used for planned collection of healthcare professional and/or consumer insights by a manufacturer/MAH, or third party acting on their behalf, on drugs and/or a disease area, for the purpose of marketing and business development.

(adopted from ICH E2D (R1))

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.

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.

Organized data collection system (ODCS):

An organized data collection system (ODCS) is an activity that gathers data in a planned manner, thereby enabling review to be performed.

We require manufacturers or MAHs to have a protocol for certain types of ODCS, for example clinical trials and non-interventional studies. In this context a protocol means a document that describes the objectives, design, methodology, statistical considerations and organization of a clinical trial or study.

For manufacturer or MAH ODCS activities that are not conducted according to a protocol, such as a sentiment analysis, or a patient support program, the manufacturer or MAH should have documentation that describes the:

1. Objectives of the ODCS activity
2. Source(s) of the data
3. Dataset that manufacturer or MAHs will collect or receive and review in order to meet the objectives of the activity detailed under item 1, including the time period that will be represented by the data
4. Method used to review the dataset to meet the objective of the activity
5. Process for collection and management of any ADRs that may be identified.

Examples of ODCS include:

- clinical trials
- non-interventional studies such as, pharmacoepidemiologic, drug utilisation studies, registries
- patient support programs
- market research programs
- manufacturer or MAH activity using a patient forum on a digital platform to assess patient perceptions of the safety of disease treatments
- product-specific sentiment analysis conducted by a manufacturer or MAH using posts on social media networking sites

(adopted from ICH E2D(R1))

Ongoing signal:

A signal that remains under evaluation at the data lock point.

(ICH E2C (R2))

Patient support program (PSP):

An organized data collection system initiated by the manufacturer or MAH:

- in which patients enroll for the purpose of supporting their use of the manufacturer or MAH's drug, or the management of their medical condition, and
- which include a mechanism for two-way communication between the manufacturer or MAH (or third party acting on their behalf) and patients or healthcare professionals.

Examples of PSPs include adherence support, disease management, and certain reimbursement programs.

PSPs:

- solicit medical information about the patient's use of a drug and/or
- will foreseeably receive medical information about the patient's use of a drug, for example, when a program involves HCP interaction with a patient to administer medication or provide medical advice.

Note:

- manufacturer or MAH-initiated programs that do not meet the criteria above (for example, delivery of a product to a patient's home, provision of vouchers or coupons) are not considered PSPs, as long as the manufacturer or MAH does not request medical information about the patient's use of a drug.
- PSPs exclude:
 - clinical trials
 - non-interventional studies, such as post-authorization safety studies which have a scientific intent or are testing a hypothesis
 - all forms of compassionate use, and
 - named patient supply
- Similar terms may also be used such as patient assistance program.

(adopted from ICH E2D(R1))

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.

Phase IV (post-market or post-authorization) clinical trials/studies:

It includes those trials that involve the use of:

- a new drug that has been issued a NOC under subsection C.08.004(1) of the Regulations, if the clinical trial is in respect of a purpose or condition of use for which the NOC was issued; or
- a drug, other than a new drug, that has been assigned a drug identification number (DIN) under subsection C.01.014.2(1) of the Regulations, if the clinical trial is in respect of a use or purpose for which the DIN was assigned.

Phase IV clinical trials are performed after the drug has been authorized by us for the market, and within the parameters of the authorized NOC or DIN application.

Potential risk:

Unexpected occurrences or undesirable clinical outcomes where scientific evidence indicates the possibility of a causal relationship with the drug and there is not enough evidence to conclude the relationship is causal.

Primary use of data:

Data generated specifically for the present study, which may be collected via:

- case report forms
- laboratory measurements
- electronic patient-reported outcomes, or
- mobile health tools.

The collection of this data may come from:

- patients,
- caregivers,
- healthcare professionals or
- other persons involved in patient care.

Product Monograph:

A product monograph is a factual, scientific document on a drug product that describes the properties, claims, indications, and conditions of use for the drug. A product monograph also contains information that may be required for optimal, safe, and effective use of the drug but should be devoid of promotional material.

Qualified healthcare professional (QHCP):

- a medically-qualified person such as a physician, dentist, pharmacist, nurse, coroner, or as otherwise specified by local regulations
- who is entitled to provide healthcare under the laws of the jurisdiction in which the person is located

Note: A QHCP can also be an individual with the appropriate healthcare education and therapeutic expertise, employed by the manufacturer or MAH.

Qualitative signal detection:

Case-by-case manual screening of each individual case report of a suspected adverse drug reaction submitted to a spontaneous reporting system that must be performed by an assessor. The assessor uses his/her human intellect to evaluate the likelihood that the adverse event was caused by the suspect drug.

(CIOMS Cumulative Pharmacovigilance Glossary: Version 1.0)

Quantitative signal detection:

Refers to computational or statistical methods used to identify drug-event pairs (or higher-order combinations of drugs and events) that occur with disproportionately high frequency in large spontaneous report databases.

(CIOMS Cumulative Pharmacovigilance Glossary: Version 1.0)

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

Risk minimization measures (or "activities"):

Interventions that:

- prevent or reduce the occurrence of adverse reactions associated with the exposure to a drug or

- reduce their severity or impact on the patient should adverse reactions occur

"Routine risk minimization measures" (or "activities") are those that apply to all drugs.

Examples include information on risks minimization in the Canadian Product Monograph, patient medication information and limitations on package size.

"Additional risk minimization measures" (or "activities") are beyond routine risk minimization measures and are needed to:

- prevent or reduce the probability of an undesirable outcome or
- reduce its severity should it occur

Examples include controlled access or distribution programs or educational programs.

Secondary use of data:

Data obtained from sources external to the present study, which include:

- historical clinical studies
- national death databases
- disease and drug registries
- claims data and
- medical and administrative records from routine medical practice.

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 drug 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 detection:

The act of looking for and/or identifying signals using event data from any source.

(CIOMS Cumulative Pharmacovigilance Glossary: Version 1.0)

Signal evaluation:

Evaluating a signal requires a multi-faceted approach:

- (a) to collect the evidence to evaluate whether there is a causal link between the event and the administration of the drug,

- (b) to determine whether the signal represents a potential or identified risk and, if this is the case, to characterize the qualitative and quantitative profile of the risk, and,
- (c) if a risk has been characterized, to communicate the risk and to propose measures aimed at preventing its occurrence or minimizing its consequences.

(adopted from CIOMS Practical Aspects of Signal Detection in Pharmacovigilance)

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.

Solicited Reports:

Reports derived from an ODCS. Manufacturers or MAHs should conduct a causality assessment for solicited ICSRs.

(adopted from ICH E2D (R1))

Spontaneous Reports:

Reports not derived from an ODCS. They are communicated by a healthcare professional or consumer to a manufacturer or MAH, regulatory authority or other organization (for example, the World Health Organization Uppsala Monitoring Center, Regional Pharmacovigilance Center). Manufacturers or MAHs should assume implied causality for spontaneous ICSRs.

(adopted from ICH E2D (R1))

Note: Also known as unsolicited reports.

True copy:

An exact verified copy of an original record.

Unusual failure in efficacy (UFIE):

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

Unexpected ADR:

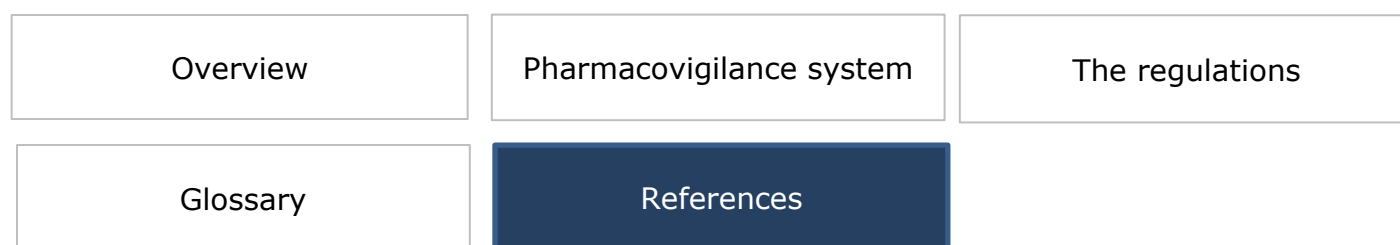
An ADR is considered unexpected when its nature, severity, specificity or frequency is either not identified, or is not consistent with the terms or description used in the Canadian product labelling, such as the:

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

(adopted from ICH E2D (R1))

DRAFT

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



Laws and regulations

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

Other Quality Documents

Health Canada Policies

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

Health Canada Guidance Documents

- Risk classification of Good Pharmacovigilance Practices (GVP) observations (GUI-0063)
- Guidance document for industry – Reporting adverse reactions to marketed health products
- Preparing and Submitting Summary Reports for Marketed Drugs and Natural Health Products - Guidance Document for Industry
- Guidance on notifying Health Canada of foreign actions
- [Submission of targeted risk management plans and follow-up commitments for prescription opioid-containing products – Guidance for industry](#)
- [Guidance on the Food and Drug Regulations for public health emergency drugs](#)
- [Submitting risk management plans guidance document](#)
- [Guidance Document: Product Monograph](#)
- [Guidance Document: Post-Notice of Compliance \(NOC\) Changes: Safety and Efficacy Document \(for pharmaceutical, biologic and radiopharmaceutical drugs for human use only\)](#)
- [Guidance document: Administrative processing of submissions and applications involving human or disinfectant drugs](#)

Other Health Canada Guidance Documents and Databases

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

International Guidance Documents

- [Periodic Benefit-Risk Evaluation Report \(ICH E2C\(R2\)\)](#)
- [Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting \(ICH E2D\)](#)
- [Post-approval Safety Data: Definitions and Standards for Management and Reporting of Individual Case Safety Reports \(ICH E2D\(R1\)\)](#)
- [MedDRA Support Documentation](#)
- [Council for International Organizations of Medical Sciences \(CIOMS\) Form I](#)
- [Practical Aspects of Signal Detection in Pharmacovigilance \(CIOMS Working Group VIII\)](#)
- [CIOMS Cumulative Pharmacovigilance Glossary \(Version 1.0\)](#)