Health Canada Santé Canada

Submitting risk management plans guidance document

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Canada

Health Canada is responsible for helping Canadians maintain and improve their health. It ensures that high-quality health services are accessible, and works to reduce health risks.

Également disponible en français sous le titre :
Ligne directrice sur la présentation des plans de gestion des risques

To obtain additional information, please contact:

Health Canada
Address Locator 0900C2
Ottawa, ON K1A 0K9
Tel.: 613-957-2991
Toll free: 1-866-225-0709
Fax: 613-941-5366
TTY: 1-800-465-7735
E-mail: publications-publications@hc-sc.gc.ca

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Foreword

Guidance documents provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. They also provide guidance to Health Canada staff on how mandates and objectives should be met fairly, consistently and effectively.

Guidance documents are administrative, not legal, instruments. This means that flexibility can be applied. However, to be acceptable, alternate approaches to the principles and practices described in this document must be supported by adequate justification. They should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As always, Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, to help us adequately assess the safety, efficacy or quality of a therapeutic product. We are committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read along with the relevant sections of the regulations and other applicable guidance documents.

Sponsors/MAHs should refer to the most up-to-date versions of the guidance documents. The guidance documents are a starting point only to help sponsors/MAHs.

Table of contents

Overview

Policy objectives

Health Canada has adopted and integrated the use of risk management plans and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2E guideline into the review of drugs in Canada. Amendments to the Food and Drug Regulations (FDR) to incorporate this long-standing practice into the regulations will come into force in April 2027.

From time to time, we review our guidance documents to make them clearer and reflect current practices and updated policy.

Improvements to this guidance document reflect our ongoing experience and the feedback we received from stakeholders, including during consultations on the agile licensing project. The improvements we have made since this guidance document was originally published will:

- support a lifecycle approach to drug vigilance
- enhance the quality of our regulatory assessments
- align drug vigilance with international best practices
- support timely access to safe, effective and high-quality drugs for people in Canada
- support ongoing evaluation of information that could have an impact on the benefits and risks of drug products

Purpose of a risk management plan

A risk management plan (RMP) is a document that:

- identifies and characterizes risks and uncertainties of a drug, such as:
  - important identified risks
  - important potential risks
  - missing information
- describes pharmacovigilance measures designed to monitor and address risks and uncertainties
- describes risk minimization measures, such as interventions designed to prevent or reduce risks
- describes methods to assess the effectiveness of those risk minimization measures and interventions

Health Canada may request RMPs for drugs when:

- there is a significant degree of uncertainty about the risks associated with the drug
- the drug presents a serious risk of injury to human health that warrants measures, other than labelling, to reduce the probability or severity of such an injury

The RMP may be used:

- to identify and characterize the risks associated with the drug and to prevent or reduce those risks or address uncertainties
- by the Minister to assess the safety and effectiveness of the drug
- as a factor in our decision to issue, suspend or remove a market authorization

For specific examples, refer to When to file a risk management plan with Health Canada.

Scope and application

This guidance document is for sponsors and market authorization holders (MAHs). It explains when and how to submit an RMP and RMP updates over the course of the lifecycle of a drug.

It also clarifies:

- what constitutes an acceptable RMP
- how to address the Canadian context, including the format for a Canadian-specific addendum
- the submission of RMP summaries, including the standard for an acceptable RMP summary format
- how to manage the submission of RMPs

The principles and practices outlined in this guidance document apply to drugs for human use (defined in section 2 of the Food and Drugs Act (FDA)) regulated under the FDR.

These include the following products that are within the scope of the ICH E2E guideline:

- pharmaceutical drugs, such as prescription and non-prescription drugs, including generic drugs
- biologic drugs as set out in Schedule D to the FDA, including:
    - vaccines
    - fractionated blood products
    - biotherapeutic drugs, including biosimilars
- radiopharmaceutical drugs as set out in Schedule C to the FDA

This document does not apply to the following products:

- veterinary drugs
- natural health products
- whole blood and blood components
- medical devices, except when they are part of a combination product submission and classified in 1 of the applicable product categories

Sponsors and MAHs should be familiar with the requirements of the FDA and the regulations for routine pharmacovigilance measures, such as these requirements from the FDR:

- adverse reaction reporting (C.01.017)
- preparing annual summary reports (C.01.018)
- providing information on serious risk of injury to human health (C.01.050)

The need for an RMP is determined on a product-by-product basis, taking into account the available information about risks and uncertainties.

Where applicable, the processes for reviewing RMPs will be compatible with and complement other regulatory activities, such as the review of market authorization submissions.

Background

We base a decision to authorize a drug for sale in Canada on evidence of its safety, efficacy and quality. The benefits of the drug must outweigh the risks within the conditions of use specified in the product labelling.

Authorization is based on the information available at the time. Information about the safety profile of the drug can change over time as more patients with varying characteristics are given the drug. For example, during the early post-marketing period, the drug might be used:

- in settings different from those studied in clinical trials
- by a much larger population in a relatively short timeframe

As an observer country at the time, Canada was a signatory to the ICH E2E Pharmacovigilance planning guideline, which was published in 2004. This guideline gives instruction in cases where there are important identified risks of a drug, important potential risks and important missing information. This includes potentially at-risk populations and situations where the product is likely to be used that have not been studied pre-approval.

Since the release of the E2E guideline, the European Medicines Agency (EMA) and other regulators have released their own guidelines to reflect the intent of the ICH guideline. They have updated them from time to time. Many sponsors/MAHs refer to these guidelines as their preferred approach.

In February 2009, Health Canada published a notice on the implementation of risk management planning. The notice gave advice on:

- key components
- acceptable formats
- submission process
- reasons, criteria and scope for RMP requests

In June 2015, we published a guidance document on the Submission of risk management plans and follow-up commitments. This document provided sponsors/MAHs with guidance on how to proceed when submitting an RMP.

In August 2020, we published a notice of clarification specifying that RMPs are not meant to restrict access to Canadian reference products. In November 2020, we published a second notice of clarification on including Canadian-specific considerations in RMPs.

When to provide an RMP

Risk management plan policies

Sponsors/MAHs are to submit a risk management plan (RMP) to Health Canada if:

- there is a **significant degree of uncertainty** about the risks associated with the drug **or**
- the drug presents a **serious risk of injury to human health** that warrants measures, other than labelling, to reduce the probability or severity of such an injury

You should submit an RMP for the following scenarios:

- when expected as part of a new drug submission (NDS), abbreviated new drug submission (ANDS) or abbreviated extraordinary use new drug submission (AEUNDS)
- when Health Canada requests one following an application seeking a drug identification number (DIN)
- with any extraordinary use new drug submission (EUNDS)
- if a supplement to a submission results in the need for a new RMP or an update to an RMP to assess the safety and effectiveness of the drug
- when Health Canada requests one post-authorization
- when you have determined that an update is necessary due to significant differences in risks or uncertainties
- the measures that you intend to take are significantly different from those in the existing plan

We have provided some further explanations and examples of when to file an RMP with us.

With a drug submission or application

An RMP helps the Minister assess the safety and effectiveness of the drug as part of drug submissions.

You are expected to evaluate and determine if you require an RMP for your product.

You are expected to file an RMP with your drug submission or application for:

- new drug submissions that include new active substances (NAS)
- generic and biosimilar drugs whose reference product has an RMP with additional pharmacovigilance measures or additional risk minimization measures
- combinations or co-packages of products where at least 1 of the components is a drug that has its own DIN with an RMP that includes additional pharmacovigilance measures or additional risk minimization measures
- a drug that is the subject of an “extraordinary use” new drug submission

We may also request in writing an RMP after you submit an application for a DIN or a submission for a notice of compliance (NOC) where:

- there is a significant degree of uncertainty about the risks associated with the drug **or**
- the drug presents a serious risk of injury to human health that warrants measures, other than labelling, to reduce the probability or severity of such an injury

We may consider that there is a **significant degree of uncertainty** about the risks associated with a drug when:

- the data we reviewed is not enough to resolve uncertainties about a drug's safety and effectiveness, for example:
    - missing information for anticipated uses, such as long-term use or in particular populations
    - risks not well characterized prior to the drug submission or application
- the anticipated use of the drug includes settings that differ from clinical trials, such as:
    - in a larger population
    - a population with additional or different risk factors, compared to the studied population
- the significance of uncertainty may vary between drug categories
    - for example, vaccines are given to large, generally healthy populations, where benefit-risk calculation may differ from that of some therapeutic drugs
        - for that reason, RMPs may be requested for some vaccines that do not contain new active substances
- there are potential risks associated with the drug, but more information is needed to monitor and characterize those risks and their impact on the drug's safety and effectiveness
    - examples of risks or uncertainties that may not be well characterized could include the potential for off-label use, long-term use or use in patients with comorbidities

We may also consider that there is a **significant degree of uncertainty** about the risks associated with a drug in the following scenarios:

- a product produced by innovative technologies may merit greater scrutiny than one made by using established, well-characterized ones
    - examples could include certain cell or gene therapies
- new information contained in a supplement to a submission introduces a significant degree of uncertainty about the drug's safety and where further monitoring and characterization may be needed due to:
    - a change in the recommended route of administration, dosage or dosage form
    - changes in the indication, such as the extension of an existing indication to a wider population or populations with unique health and safety needs
    - new conditions of use, ranging from administration by a health care provider to self-administration in the home

Due to the uncertainty surrounding these risks, an RMP may be requested to further study, characterize and manage the risks.

Health Canada may consider that the drug presents a **serious risk of injury to human health** that warrants measures, other than labelling, to reduce the probability or severity of such an injury when:

- a serious risk has been identified and characterized and where additional pharmacovigilance measures or additional risk minimization measures or interventions may be needed, to prevent or minimize the risk or for the benefits of the product to outweigh its risks
    - examples could include relevant risks identified from reports of adverse reactions in clinical trials, epidemiological studies and real-world evidence, including issues emerging from real-world use (off-label use, medication errors)
- the drug is a member of a class of drugs with known safety concerns or uncertainties for which additional pharmacovigilance measures or additional risk minimization measures may be in place
    - additional risk minimization measures could include physician or patient educational materials, controlled access or distribution
- a drug previously associated with actions such as cancelling a DIN or discontinuing its sale due to a serious safety issue or significant uncertainty

- for an authorized product with or without an RMP for which a supplement to a submission is submitted to support a significant change to a label's safety information, such as to add:
    - information on the characteristics of a risk
    - new recommendation for risk mitigation, such as testing and monitoring
    - new information stemming from a pharmacovigilance activity
- for an authorized product with or without an RMP for which a supplement to a submission is submitted to support a significant change to the packaging that could lead to dosing or medication errors, such as:
    - a change in packaging

For a discussion of "serious risk", consult:

- annex A of the Guide to authorities under the Protecting Canadians from Unsafe Drugs Act (Vanessa's Law)

If you have questions about submitting an RMP to Health Canada, contact the Regulatory Project Management Office, Marketed Health Products Directorate early on in the application process.

Pre-submission meetings

Before filing a submission or application, you can request a pre-submission meeting to discuss all aspects of your submission, including RMPs.

For help:

- refer to the Guidance document: Management of drug submissions and applications for instructions on how to request pre-submission meetings
- request a pre-submission meeting, if needed, and indicate in the request that you wish to discuss items related to the RMP, if applicable

During a pre-submission meeting, MHPD representatives will provide appropriate guidance on the content and format of the RMP, based on the information provided in the meeting package. You may:

- include a draft RMP in the data package for a pre-submission meeting **or**
- provide an outline of the RMP or any potential questions about the RMP

An RMP that is requested as part of the submission or application should be included with the submission package. You are encouraged to include a rationale if you consider that an RMP is not needed as part of the submission.

Generic and biosimilar drugs

You should file an RMP with the submission or application for a generic or biosimilar drug whose reference product has an RMP with additional pharmacovigilance measures or additional risk minimization measures, such as:

- registries
- controlled access or distribution
- post-market safety or utilization studies
- distribution of educational materials for patients or health care providers

Sponsors/MAHs of a generic or biosimilar drug should:

- compare the risk profile of their drug to the reference product **and**
- consider additional pharmacovigilance measures or additional risk minimization measures accordingly

Health Canada may also request an RMP for generic or biosimilar drugs when there are unique safety issues associated with the drug.

We encourage you to review the information available for the reference product in the Drug Product Database or the Canadian Product Monograph, before you submit your drug submission or application. This will help you determine whether the reference product has additional pharmacovigilance measures or additional risk minimization measures. For reference products with additional measures, if an RMP summary is available, Health Canada will provide it upon request.

As part of your RMP, you are expected to consider the need for similar additional pharmacovigilance measures or additional risk minimization measures for the drug. Provide a description of the measures if appropriate. If the additional measures for your generic or biosimilar RMP differ from the reference product RMP, provide a rationale.

If you have questions about submitting an RMP to Health Canada, contact the Regulatory Project Management Office, Marketed Health Products Directorate early on in the application process.

Administrative submissions

For submissions that meet the criteria for administrative processing, post-market requirements, including RMP elements, are expected to continue as per previous authorization.

For more information, consult:

- Guidance document: Administrative processing of submissions and applications involving human or disinfectant drugs

Post-market RMP submissions

Health Canada may **also** request an RMP for a drug for which a DIN has been assigned when no RMP has been submitted to us before.

We will make our decision on a product-by-product basis, depending on information available at the time. Our request may be part of an ongoing review to support informed regulatory decision-making about the drug, including decisions about its safety and effectiveness.

We may request an RMP for a drug that has already been assigned a DIN, when there is a **significant degree of uncertainty** about the risks associated with the drug. For example:

- a drug is associated with actions subsequent to authorization, such as suspension of a NOC or stop sale, especially if the action was linked to a serious safety issue or significant uncertainty
- an emerging serious safety issue of significant potential risk is confirmed from a signal assessment that requires further characterization to identify how the risk will impact the drug's safety and effectiveness
- a major new safety concern is found in a product from the same class or there is evidence of an off-label use for which the risks are potentially serious but poorly characterized

We may also request an RMP for drugs that have already been assigned a DIN, when the drug presents a **serious risk of injury to human health** that warrants measures, other than labelling, to reduce the probability or severity of such an injury. For example:

- an emergent serious risk has been identified and additional pharmacovigilance measures or additional risk minimization measures may be needed to prevent or minimize the risk
- a safety signal or significant change identified in what is known about the risks of the drug

You should provide the RMP within the timeframe specified in the request. You may request an extension for our consideration, along with a rationale for the request, if needed.

Risk management plan updates

You should submit an update to the RMP for a drug for which a DIN has been assigned if the currently known risks associated with the drug, or uncertainties about those risks, are **significantly different** from those described in the existing RMP. This is because the existing RMP may no longer fulfill its purpose, which is to identify and characterize the risks associated with the drug and prevent or reduce those risks or address uncertainties.

RMP updates should be submitted as soon as feasible.

Examples of risks and uncertainties that are significantly different:

- new or heightened risk or uncertainty
    - new emerging or serious post-market safety issue is identified
    - new relevant serious safety risk is identified for a similar product in the class
    - new or increased risk from medication error, accidental exposure or off-label use
- new or expanded target population, for example, as a result of a new indication
- new information in the form of a safety signal or important potential risk information
- new evidence (qualitative or quantitative) about risks or uncertainties as a result of risk-monitoring or risk-characterization activities
- change to the safety specification when another regulator has approved the addition, removal or reclassification of a safety concern

Risks and uncertainties may be identified from a number of sources, such as:

- final study results that confirm a safety risk
- an annual summary report under section C.01.018 of the Food and Drug Regulations (FDR)
- an assessment ordered under section 21.31 of the Food and Drugs Act (FDA)
- an issue-related summary report under section C.01.019 of the FDR
- a foreign regulatory action (for example, reported under section C.01.050 of the FDR)
- filing of a supplement to a submission under section C.08.003 of the FDR

You should also submit an RMP update when the measures that you intend to take to address and monitor the uncertainties about a drug's risks, or to prevent or reduce those risks, differ significantly from those described in the existing plan. For example:

- new additional pharmacovigilance measures or new additional risk minimization measures are added
- additional pharmacovigilance measures or additional risk minimization measures are removed
- additional pharmacovigilance measures or additional risk minimization measures are significantly altered
- evaluation of the effectiveness of the additional risk minimization measures has changed
- elements of study protocols (objectives, population or due date of final results) for any of the studies requested by Health Canada and listed in the existing RMP or the Canadian-specific addendum have changed
- measures included in the existing RMP to identify and characterize risks associated with the drug and to prevent or reduce those risks or address uncertainties are no longer sufficient

You should also submit an RMP update if a change to a risk minimization tool (RMT) would have a significant impact on the success or objective of the additional measure.

The following changes are not considered significant:

- changes made to the RMP that are not related to the conditions of use outlined in the Canadian product monograph, or the risks, uncertainties or additional pharmacovigilance measures or additional risk minimization measures described in the existing RMP
- administrative changes, including routine maintenance or structure, layout or format changes to RMTs, unless these have an impact on the:
    - implementation of the measures contained in the RMP
    - content of the RMP summary, when one is included in the existing plan

However, you should assess if changes made to an RMP in a foreign jurisdiction or to the reference RMP are relevant to:

- the safety specification
- additional pharmacovigilance measures **or**
- additional risk minimization measures

You should assess if the following are sufficient:

- detailed description of the risks in the RMP
- pharmacovigilance plan to address and monitor the uncertainties about risks associated with the drug
- risk minimization measures to prevent or reduce the risks associated with the drug

You should provide an updated RMP if your assessment shows a significant difference to the safety specification or to the additional pharmacovigilance measures or additional risk minimization measures.

For generic and biosimilar products, you should review available information on the reference product to determine if significant updates have been made to the RMP for that reference product. If this is the case, you may need to submit an updated generic or biosimilar product RMP.

If the Canadian reference product has been discontinued, you are encouraged to review relevant available information and to monitor developments that could impact your RMP, when available.

Products with dormant DINs may still meet the threshold that would warrant an update to an RMP. Until products have been discontinued, the RMP update principles continue to apply.

If you have questions about submitting an RMP to Health Canada, contact the Regulatory Project Management Office, Marketed Health Products Directorate early on in the application process.

Updates requested by the Minister

Health Canada may request an updated RMP when the Minister has reasonable grounds to believe that the:

- risks associated with the drug or the uncertainties relating to them are significantly different than those that are described in the existing RMP
- drug presents a serious risk of injury to human health that warrants that measures that are significantly different than those described in the existing RMP be taken to reduce the probability or severity of such an injury

Examples of measures to reduce the probability or severity of a serious injury:

- risk communications
- patient or health care professional education
- patient testing and monitoring
- controlled access or distribution
- pregnancy prevention programs

Generally, the Minister would request such updates to an RMP when the existing RMP is no longer sufficient to:

- identify and characterize the risks associated with the drug and to prevent or reduce those risks or address uncertainties **or**
- assess the drug's safety and effectiveness

You should provide the RMP update within the timeframe specified in the request. You may request an extension for our consideration, along with a rationale for the request, if needed.

Preparing and submitting an RMP

What to include in your risk management plan

All risk management plans (RMPs) submitted to Health Canada should meet a standard that is acceptable to the Minister.

To meet the standard, the RMP should consider the Canadian context and contain sufficient information to enable the Minister to:

- identify and characterize the risks associated with the drug **and**
- conclude that the plan, if implemented, would prevent or reduce those risks or address uncertainties associated with the drug

The RMP should describe the:

- drug and what it is used for
- risks and uncertainties of the drug in detail
- measures you intend to take to address the uncertainties and monitor the situation in detail
    - for example, the occurrence of negative health outcomes associated with the uncertainties, their contributing factors and the outcomes of the measures used to address them
- measures you intend to take to prevent or reduce the risks in detail
- plan for evaluating the effectiveness of these measures

It should also include a summary of the plan's contents, in English and French.

The information should be included within the standard sections of an RMP:

- product overview
- safety specification
- pharmacovigilance plan
- risk minimization measures, including evaluation of the effectiveness of risk minimization measures
- summary

RMP note to reviewer

An RMP note to reviewer should accompany all RMPs, RMP updates and other RMP-related materials.

Submit the RMP note to reviewer under Module 1.3.8.2 along with the RMP.

The RMP note to reviewer is not meant to replace the general note to reviewer relevant to the entire submission (for example, guidance on the location of a particular document within the submission or reference of the product by a foreign trade name). Submit the general note to reviewer under Module 1.0.7.

For more information, consult:

- Guidance document: Preparation of regulatory activities in electronic common technical document (eCTD)

The RMP note to reviewer should include:

- the purpose of the submission
- submission details such as the version number, final sign-off date and data lock-point (if applicable)
- additional information such as the status of review of the submitted documents in other jurisdictions (if applicable) and other details that would aid the review

Find more information on preparing an RMP note to reviewer.

Canadian-specific addendum

You do not need a Canadian-specific addendum if you have:

- prepared the RMP specifically for Canada, using an acceptable format
- considered the Canadian context in the reference RMP

Include in the RMP or Canadian-specific addendum any Canadian-specific considerations, as well as a detailed description of how the information and measures apply to Canada.

Examples of special considerations for the Canadian context and related to medical practice or populations in Canada:

- information on Canadian patient exposure
- genetic or extrinsic factors that are specific to the Canadian population and that are relevant to the indication or to the risk characterization
- the epidemiology of the medical conditions or risk factors that reflect the authorized indications in Canada
    - for example, Canadian epidemiology data such as incidence rate and prevalence in Canada for the proposed indicated population, including a breakdown of that epidemiological data by groups relevant to Canada (such as sex, age, race or ethnicity)
- post-authorization experience in Canada
- important public health issues specific to Canada and specific measures needed to address, monitor, reduce or prevent them

Also include in the Canadian-specific addendum:

- safety issues specific to Canada
- pharmacovigilance measures in the Canadian context or setting
    - could involve monitoring Canadian adverse events from your database and reconciling these events with adverse reactions in the Canada Vigilance Database
- risk minimization measures and evaluation of their effectiveness in the Canadian context or setting
- appropriate milestones and timelines for reporting on additional pharmacovigilance measures and additional risk minimization measures that are applicable to Canada

Find more information on preparing a Canadian-specific addendum.

RMP summary

Include a summary as part of your RMP to meet the standard acceptable to the Minister. Health Canada will consider the RMP summary as part of the RMP review. You are expected to incorporate changes to the summary section of the RMP, as needed, as changes to the RMP occur during the review process.

The RMP summary should include an introduction as well as information on:

- the drug and what it is used for
- risks and uncertainties associated with the drug and measures to:
    - prevent or reduce the risks
    - address and monitor the uncertainties

This summary should reflect the Canadian context and include Canadian-specific considerations.

Write the summary in clear and concise language that is accessible for many users, including:

- industry
- academia
- health care providers
- interested members of the public
- health technology assessment bodies
- patient safety and other stakeholder associations
- government agencies or departments and regulatory licensing bodies

To respect official language standards, you are encouraged to provide the summary in both English and French, along with an attestation that both language versions accurately reflect the content of the RMP. The summary in the second language, along with the attestation, can be provided during the review process. We will advise you in writing (for example, in a clarification request) once the review has reached a stage where the summary in the other language should be submitted.

You are responsible for verifying that the RMP summary does **not** contain confidential business information that you do not want made public.

To support transparency and increase access to information on drugs, Health Canada will make these summaries available upon request.

Some manufacturers voluntarily post Canadian drug product information on their websites, including the Canadian Product Monograph. To further support transparency and access to information on drugs, you are encouraged to post the RMP summary on your Canadian website, in both official languages.

Find more information on preparing an RMP summary.

Acceptable risk management plan document format

RMPs are acceptable in:

- the EU RMP format
- other formats if they meet the standard outlined in this guidance document

You should consult the European Medicines Agency's Guidance on the format of the risk management plan (RMP) in the EU, in integrated format.

Note: If you use a reference RMP, you should include a Canadian-specific addendum containing information specific to the Canadian context. If you prepare the RMP specifically for Canada, you must consider the Canadian context throughout the RMP.

Procedures to file an RMP

There are currently 2 acceptable filing formats for RMPs or related documents:

- electronic common technical document (eCTD) format
- non-eCTD electronic-only format

For submissions in the eCTD format, consult:

- Guidance document: Preparation of drug regulatory activities in the electronic common technical document format

For submissions in the non-eCTD electronic-only format, refer to the structure template recommended in:

- Guidance document: Preparation of regulatory activities in the "non-eCTD electronic-only" format

For information on submission requirements and general procedures on how to file pre-market submissions, consult:

- Guidance document: The management of drug submissions and applications (new drug submissions including NDS, SNDS, ANDS and SANDS, and DIN applications)
- Guidance document: Information and submission requirements for biosimilar biologic drugs (biosimilars)

General considerations

An RMP reflects both clinical and non-clinical safety data. It should be updated throughout the drug's lifecycle as discussed and agreed upon with Health Canada.

When submitting RMPs, you should:

- submit an RMP for each brand name that covers all the indications for that product
    - if you believe this is not appropriate or feasible for a specific drug or medicinal ingredient, you should provide a rationale and communicate with us early in the process
- submit the most recent version of the reference RMP available
    - if the reference RMP is being reviewed in another jurisdiction, provide the status of the review process, if available, in the RMP note to reviewer
    - submit a revised reference RMP during the regulatory review process if the approval in another jurisdiction results in updates to the reference RMP
        - clearly identify the revisions from the RMP currently under review
- provide RMP review reports from foreign regulatory authorities, if available
- include available real world data if marketed in Canada or elsewhere
- include relevant market experience of the drug in the RMP if it is already marketed elsewhere (for example, with the same formulation and medical ingredient)
    - examples of market experience include regulatory or safety issues, medication errors specific to formulation, uses (home or hospital, on-label or off-label) and approved indications
    - we may ask for the most recent Periodic Benefit-Risk Evaluation Report (PBRER) or Periodic Safety Update Report (PSUR), if available, for a drug marketed elsewhere, to complement or supplement exposure and safety data provided in the RMP
- examine the potential for new or heightened safety concerns for combination drugs compared to the individual products
- provide a rationale for RMP updates, supported by scientific evidence, for changing, adding or removing any safety concerns, additional pharmacovigilance measures or additional risk minimization measures from the previous RMP version submitted to Health Canada
    - for changes that have been implemented or planned in another jurisdiction or country, include the evidence that supported those changes and an evaluation of any relevant Canadian data that supports a similar change in Canada
- provide a rationale where additional pharmacovigilance measures or risk minimization measures are proposed or implemented in major jurisdictions (such as the European Union or US) but not in Canada
- reference the most recent version of the Canadian product monograph

For RMP updates, submit clean and track change versions of the reference RMP, Canadian-specific addendum (if revised), and RMP summary, unless the changes involve a complete format change.

If there are simultaneous RMPs submitted for review, include final changes from the concurrent reviews when available.

If the RMP is part of a pre-market drug submission or application, the applicable timelines for those submissions apply. Regulatory correspondence for RMPs attached to a submission should include a reference to the control number.

Note: Elements of RMPs, such as controlled access or distribution programs, are not intended to restrict access to Canadian reference products (CRPs) for generic drug manufacturers for the purposes of conducting comparative testing. Any RMP elements should not be used as a reason to:

- delay or hinder comparative testing by generic products **or**
- hinder their ability to enter the market

You should have an adequate system in place to manage your commitments for RMPs. This system can be part of your global systems and processes. It should:

- adapt to scientific and technical progress throughout the lifecycle of the drug
- include proper documentation of all measures taken
- ensure that all persons involved in quality systems' procedures and processes be appropriately qualified and trained
- ensure that any third parties you use to assist with pharmacovigilance measures are able to comply with the measures

For more information on adequacy of a pharmacovigilance system, consult:

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

Contact information for submitting an RMP or other related documents

You should submit RMPs or other related documents to the Office of Submissions and Intellectual Property (OSIP) via the Common Electronic Submissions Gateway (CESG) using the regulatory enrolment process (REP).

For transactions in e-CTD format, consult:

- Preparation of regulatory activities in the eCTD format
- The regulatory enrolment process (REP): Drugs for human/veterinary use and disinfectants

For transactions in non-eCTD format, consult:

- Preparation of regulatory activities in the non-eCTD format
- The regulatory enrolment process (REP): Drugs for human/veterinary use and disinfectants

Do **not** file the RMP using a supplement to a submission when requested post-authorization or for RMP updates, **unless** it is needed to assess the drug's safety and effectiveness in relation to the supplement to a submission being filed.

Review of risk management plans

Review bureaus at the Marketed Health Products Directorate (MHPD) conduct the review of RMPs, updates and other related materials.

RMPs included with a drug submission or application

Health Canada will screen the submission. If you do not provide an RMP or if you provide a rationale in the absence of an RMP, but we determine an RMP should be submitted, we will request one.

If we identify issues or have questions during our review, we will send a communication (such as a clarification request) to you, including the timelines for response.

Once we have completed our review, we will notify the appropriate pre-market directorate of the result.

We will provide you with written notice to confirm if the RMP included in the submission is acceptable.

For information on the timelines to respond and RMPs included with a drug submission or application, including the screening process, consult:

- Guidance document: The management of drug submissions and applications

Post-market RMP submissions

Health Canada may send a letter to you at any time to request an RMP or an update to an existing RMP. You should submit the requested RMP or RMP update within the timelines specified in our request.

You should also submit an update to an RMP as soon as feasible if the risks or uncertainties, or the measures you intend to take, are significantly different from those described in the existing plan.

If we identify issues or have questions during our review, we will send a communication (such as a clarification request) to you, including the timelines for response. The timeline to respond is usually between 15 and 30 calendar days. These are guidelines only and can be adjusted based on the nature of the request. Any responses to these clarification requests should be sent to the MHPD.

When we have completed our review, we will inform you of the outcome.

Status requests

The MHPD will review the RMP and inform you of the outcome.

For information on the timelines of a drug submission, consult:

- Guidance document: The management of drug submissions and applications

Contact the regulatory project manager in MHPD if you have questions about the RMP part of your submission.

To support transparency, information on the status of a review that is not part of a drug submission or application will continue to be included in the industry access to the submission tracking system.

We will share the final RMP review report with you upon request.

Acceptability and implementation

To be deemed acceptable for the Canadian context, the RMP should contain sufficient information to enable the Minister to:

- identify and characterize risks **and**
- conclude that the plan, if implemented, would prevent or reduce those risks and address uncertainties associated with the drug

As part of the review, we will determine acceptability based on the following:

- Canadian context sufficiently reflected within the RMP
- accuracy of the description of the drug compared to the information already known to the Minister
- risks and uncertainties described in sufficient detail
- if the measures the manufacturer intends to take are sufficient to address and monitor the uncertainties related to the risks associated with the drug and to prevent or reduce those risks
- pharmacovigilance plan and risk minimization measures described in sufficient detail
- plan to evaluate the effectiveness of the measures to prevent or reduce the risks described in sufficient detail and sufficient to evaluate those measures
- accuracy of the summary in reflecting and summarizing the content of the RMP, in English and French

The RMP should include sufficient detail on the timing of implementation of measures, evaluation of measures and reporting.

In our review, we will also consider whether the plan, including the proposed measures, is feasible and reasonable.

The proposed measures should be implementable in Canada and consider the Canadian context:

- federal, provincial and territorial regulations
- funding and resources for activities (burden)
- ethical obligations and constraints such as practice standards and codes of professional conduct
- local availability of technical and medical expertise and equipment to conduct activities (remote or Indigenous communities)
- regulation of health care providers in Canada (colleges, jurisdictions), including legal obligations and constraints

The measures in an RMP should not unduly limit access or distribution of products to patients and health care providers.

To ensure the proposed measures are feasible, reasonable and implementable in Canada, you may wish to consult interested and affected parties, such as Canadian health care providers (for example, physicians, nurses, pharmacists).

Following acceptance, we expect you to implement and perform the pharmacovigilance and risk minimization measures in accordance with the descriptions and timelines outlined in the RMP. You are also expected to implement and perform any measures outlined in subsequent RMP updates found to be acceptable.

Health Canada will confirm follow-up actions outlined in the RMP, as needed.

The Minister may use authorities under the FDA or FDR to respond to risks and uncertainties that are not sufficiently addressed by an RMP.

These authorities include:

- issuing a request for information subject to a stop sale under C.01.013 of the FDR
- ordering a labelling or packaging change under 21.2 of the FDA
- ordering an assessment under 21.31 of the FDA
- ordering activities under 21.32 of the FDA, such as tests, studies or monitoring

Record-keeping

You should keep a copy of the RMP, as well as records of the decisions you made when creating and updating the plan. You should also keep the information you relied on when making those decisions, and have them readily available when we request them.

Document all decisions related to creating or updating the RMP, including those that concern:

- the submission of an updated RMP
- the feasibility of the measures outlined in the RMP
- any modifications made to the RMP (for RMP updates)

Examples of information that you may rely on when making these decisions could include:

- documentation of measures described in the RMP, such as:
    - process approvals
    - operating procedures
- information supporting a change to the measures outlined in the RMP
- data supporting the effectiveness of the measures outlined in the RMP
- information supporting a significant difference to risks and uncertainties
- evidence used to support the creation of initial and subsequent versions of RMPs

The RMP outlines the measures that you intend to take, as well as the manner in which you intend to evaluate the effectiveness of those measures. For this reason, you should also keep:

- documentation supporting the implementation and operation of the RMP
- information on the effectiveness of the measures outlined in the RMP
- materials that support pharmacovigilance measures or risk minimization measures, including implementation of such measures, such as:
    - protocols
    - brochures
    - educational materials
    - follow-up questionnaires
    - contractual agreements
    - interim and final reports
    - evidence of completion of the activity

We recommend that you keep the RMP and records for at least 5 years after the drug has been discontinued in Canada, unless other regulatory requirements for documentation apply.

You are also responsible for preserving data integrity. Based on how documents are preserved, you should consider having processes to:

- restrict file access to relevant personnel
- validate computerized systems and audit trails
- make periodic backups for electronic documents
- ensure documents are preserved in disaster situations

For more information on record-keeping best practices, review:

- EMA GVP Module V (section V.B.12)
- Good pharmacovigilance practices (GVP) guidelines (GUI-0102)

RMP note to reviewer template

Include the note to reviewer in Module 1.3.8.2 with the submission of all RMPs and RMP-related materials.

RMP note to reviewer

Purpose of RMP submission	
RMP	Indicate reason for submission (examples provided) • RMP included with new drug submission that includes a new active substance • RMP included with generic or biosimilar drug whose reference product has an RMP with additional risk minimization measures or additional pharmacovigilance measures • RMP included with combinations or co-packages of products where at least 1 of the components is a drug that has its own DIN with an RMP that includes additional risk minimization measures or additional pharmacovigilance measures • Updated RMP submitted with a supplement to a submission in support of a new indication • Updated RMP submitted due to significant change in degree of uncertainty or serious risk of injury to human health • RMP submitted following Health Canada's request under control number, letter dated (dd/mm/yyyy)
Related materials	Specify materials and indicate reason for submission (examples provided) • Document (for example, risk minimization tool) in support of RMP submission or submitted as requested by Health Canada under control number, letter dated (dd/mm/yyyy) • Document (for example, risk minimization tool or study protocol) submitted due to a new or heightened risk or uncertainty • Document (for example, foreign review report) in support of aligning with RMP submitted to other foreign authorities

RMP submission details		
If applicable, indicate the RMP submitted within current transaction	Canadian RMP or reference RMP with Canadian-specific addendum	☐ Canadian RMP ☐ Reference RMP with Canadian-specific addendum Include versions, final sign-off dates and data lock points
If applicable, indicate the most recently approved RMP by Health Canada	Canadian RMP or reference RMP with Canadian-specific addendum	☐ Canadian RMP ☐ Reference RMP with Canadian-specific addendum Include Health Canada approval date, control and version numbers of document (if applicable)
If applicable, provide details on any related submissions currently undergoing Health Canada's review (including other versions of the RMP)		Include control and sequence numbers Indicate if the product monograph, product packaging or product labels are currently under review with Health Canada
If applicable, provide details on whether any of the documents submitted are approved or undergoing review in other jurisdictions		Specify whether the reference RMP or other RMP-related material has been submitted to another jurisdiction, identify the jurisdiction and clarify whether the submitted material is under review (with anticipated approval date) or has been approved (with date of approval).
Additional notes		
Additional information for reviewers		Indicate any additional details that will guide the reviewer, for example: • if there are planned actions in Canada, such as an intention to submit a safety update for the Canadian product monograph as a supplement to a submission • high-level rationale for significant changes to an existing RMP • rationale for differences between the reference RMP and the Canadian-specific addendum or to remove a safety concern, risk minimization measure or pharmacovigilance measure • rationale if a generic or biosimilar RMP differs from the innovator RMP

Canadian-specific addendum template

A Canadian-specific addendum should address:

- risks or uncertainties that are unique to the Canadian context
- measures that the manufacturer intends to take that are unique to the Canadian context

Information may vary, however, a Canadian-specific addendum should contain the following sections:

- cover page
- safety specification
- pharmacovigilance measures in Canada
- risk minimization measures and evaluation of their effectiveness in Canada
- references
- appendices

However, indicate if the sections:

- do not apply
    - indicate that the section is not applicable, along with a rationale
- do not have Canadian specific content
    - indicate that the Canadian context does not differ from that in the reference RMP, there are no risks or uncertainties unique to the Canadian context or the measures the manufacturer intends to take described in the reference RMP apply to the Canadian context

Cover page

The cover page of the Canadian-specific addendum should include:

- a title that includes the name of the product or the proposed brand name and that it is a Canadian-specific addendum to the reference RMP
- the proper name or non-proprietary name of the drug in final dosage form
- the version, date of final sign-off and data lock point for the current Canadian-specific addendum
- the version, date of final sign-off and data lock point for the reference RMP

Safety specification

In this section, provide:

- the Canadian epidemiology
- a summary of Canadian-specific safety concerns

Epidemiology of the indications and target populations relevant to Canada

Note: This section may have reduced content for certain products, such as generics or biosimilars, or certain well-characterized non-prescription drugs.

Indication

Provide the current or proposed indications according to the Canadian product monograph.

Epidemiology in Canada

Provide a brief summary of the Canadian epidemiology of the product's indication (incidence and prevalence in Canada), including main existing treatments available in Canada. Specify any notable differences from the reference RMP, including:

- the epidemiology of the medical condition
- risk factors for the authorized indication in Canada
    - for example, in cases where it is different from the authorized indication in other major jurisdictions, such as Europe and the US
- when the drug is meant to be used by a small group of patients in Canada

Details of target population

Provide any relevant information such as demographics of the target population and the setting for use of the product in Canada, including:

- available information about population characteristics, such as:
    - age or age categories such as pediatric or geriatric
    - sex or gender
    - underrepresented or underserved populations (when relevant for assessment of safety and risk management), such as:
        - racialized or ethnic minorities
        - pregnant or lactating people
        - patients with psychiatric disorders
        - patients with relevant comorbidities
- the intended prescriber for the drug and any considerations related to the medication use process, from prescribing to dispensing to administering and monitoring the drug
- the setting in which the drug should be used, such as:
    - hospitals
    - outpatient clinics
    - at home
- potential challenges to risk management
    - for example, remote locations and rural communities may present challenges for monitoring or follow-ups
- particular risk management considerations for specified groups or populations, such as Indigenous populations
- potential for medication errors
- misuse or illegal use
- potential challenges related to availability of technologies, devices or supplies in Canada required for risk management or use of the product

Post-authorization experience

Include cumulative patient exposure in Canada since product launch, if applicable (the global cumulative patient exposure should be included in the reference RMP).

The cumulative patient exposure in Canada must be presented separately from the global information. If the Canadian-specific data has been included separately in the reference RMP, this should be specified.

If needed, Health Canada may request an annual summary report under C.01.018 of the Food and Drugs Regulations (FDR).

Canadian-specific safety concerns

Indicate whether the safety concerns listed in the reference RMP are applicable to Canada. If not, explain why.

If there are Canadian-specific safety concerns that are not listed in the reference RMP, provide a detailed description of the safety concerns.

Provide a clear justification, including scientific evidence, if there are safety concerns that:

- have been changed or amended
- were included in the previous version and have now been removed
- were included in the reference RMP that are not considered relevant in Canada

It's not enough to cite acceptance of such a change by another regulator without providing a rationale.

If additional safety concerns need to be considered or a risk is reclassified or removed, describe the concerns and provide the underlying scientific rationale for any changes.

Examples of safety concerns specific to the Canadian context may include:

- genetic, external or other factors that are unique to the population, such as:
  - age
  - sex
  - gender
  - race
  - ethnicity
- the proposed or approved indications
- the expected use of the product, including the:
  - potential for off-label use
  - potential for medication errors
  - potential harm from an overdose
  - potential for transmission of infectious agents
  - risks in pregnant and lactating people or in children
  - risks associated with other members of the pharmacological class

If applicable, include information on clinical trial exposure in Canada.

Sample summary table of safety concerns in Canada

Summary of sponsor's safety concerns

Safety concern	Reference RMP	Canadian-specific addendum
Important identified risks		
-	-	-
-	-	-
Important potential risks		
-	-	-
-	-	-
Missing information		
-	-	-
-	-	-

Pharmacovigilance measures in Canada

In this section, provide:

- the routine pharmacovigilance measures in Canada
- the additional pharmacovigilance measures in Canada
- a summary table of pharmacovigilance measures in Canada

Also, in this section, confirm whether all pharmacovigilance measures, including routine measures and additional measures, listed in the reference RMP apply to Canada. Provide an explanation if the pharmacovigilance measures are not relevant.

Routine pharmacovigilance measures in Canada

Provide information on the routine pharmacovigilance measures in the Canadian context, including:

- details of pharmacovigilance practices since product launch
- Canada-specific monitoring of adverse events, including search strategy, and reconciliation with the Canada Vigilance Database

Provide an explanation if these routine pharmacovigilance measures in Canada differ from the reference RMP.

Describe the routine pharmacovigilance measures that have been or will be implemented to address these safety concerns if there are Canada-specific safety concerns.

Refer to the sections in the reference RMP, if applicable.

Additional pharmacovigilance measures in Canada

Provide information on the additional pharmacovigilance measures in the Canadian context, such as:

- synopsis of studies
- copies of the study protocols for studies requested in Canada or with Canadian sites
    - or with potential Canadian sites if the study has not yet been approved elsewhere or has not yet started

For each additional pharmacovigilance measure listed in the reference RMP, state how it is relevant to the Canadian context at the time of submission. Include how:

- findings from the activity will inform the risk characterization and RMP updates in Canada
- milestones and timelines for reporting, including any deliverables, will be provided to Health Canada
- the pharmacovigilance measure is conducted in Canada, for example:
    - study has Canadian sites
    - registry can enroll Canadian patients

Provide a description and a detailed reason for these differences if:

- additional pharmacovigilance measures only apply to Canada **or**
- international pharmacovigilance measures differ from those proposed for Canada

Refer to the sections in the reference RMP, if applicable.

If there are Canadian-specific additional pharmacovigilance measures that are not listed in the reference RMP, provide a detailed description of these measures using the same format as in the reference RMP.

Sample summary table of pharmacovigilance measures in Canada

Study and status	Summary of objectives	Safety concerns addressed	Milestones (Canadian context)	Due dates and deliverables
Important identified risks				
-	-	-	-	-
-	-	-	-	-
Important potential risks				
-	-	-	-	-
-	-	-	-	-
Missing information				
-	-	-	-	-
-	-	-	-	-

Risk minimization measures in Canada and evaluation of their effectiveness

In this section, provide details of:

- the routine risk minimization measures in Canada
- the additional risk minimization measures in Canada, including the plans to evaluate the effectiveness of risk minimization measures in Canada
- a summary table of risk minimization measures in Canada

Also, in this section, confirm whether all risk minimization measures, including routine measures and additional measures listed in the reference RMP apply to Canada. Provide an explanation if they do not apply to Canada.

Routine risk minimization measures in Canada

Provide detailed information on the routine risk minimization measures in Canada for the safety concerns that apply to Canada at the time of submission. Provide an explanation if these measures differ from the reference RMP.

When discussing routine risk minimization measures in Canada, refer to the most recent version of the Canadian product monograph, product packaging and product labels. Indicate in the RMP note to reviewer if the Canadian product monograph, product packaging or product labels are currently under review with Health Canada.

Additional risk minimization measures in Canada

Provide information on the additional risk minimization measures in the Canadian context. This could include a history of those additional measures that may have been discontinued.

For these measures:

- describe the risk minimization tool (RMT) that is intended to be used
- include the objective and rationale
- describe their implementation including the target audience, how and when the tools or material will be disseminated
    - if applicable, compare additional risk minimization measures proposed in Canada with those in other jurisdictions and provide a reason for using a different approach
- describe methods to evaluate their effectiveness and include timelines for reporting
    - if applicable, compare the manner used to evaluate the effectiveness of the risk minimization measures in Canada with the manner used in other jurisdictions and, if they differ, explain the reason for these differences

Include in the appendix copies of any RMTs used in risk minimization measures.

Provide a rationale if an RMT is not available at the time of submission, as well as a timeline for completing the preparation of the tool and its submission to Health Canada for review.

If an RMT is not available at the time of submission, Health Canada may request a draft or mock-up of the tool during the review, as needed.

Sample summary table of additional risk minimization measures in Canada

Safety concern	Routine risk minimization measures (for example, product labelling and packaging)	Additional risk minimization measures (for example, controlled access or distribution program, educational materials)	Evaluation of the effectiveness of additional risk minimization measures (for example, evaluation plan and criteria for success)
Important identified risks			
-	-	-	-
-	-	-	-
Important potential risks			
-	-	-	-
-	-	-	-
Missing information			
-	-	-	-
-	-	-	-

References and appendices

You may use references and appendices in the Canadian-specific addendum to provide further information.

References

In this section, provide any references used in the Canadian-specific addendum.

Appendices

Include as an appendix any materials referred to within the Canadian-specific addendum. Examples include:

- study protocols for planned Canadian pharmacovigilance studies
- pharmacovigilance materials such as adverse event and medication error follow-up questionnaires implemented or to be implemented in Canada
- risk minimization tools used in Canada

RMP summary template

The RMP summary should include the following sections:

- an introduction
- the drug and what it is used for
- risks and uncertainties associated with the drug and measures to:
    - prevent or reduce the risks
    - address and monitor the uncertainties

If 1 or more of the sections do not apply, you should still include them in the RMP summary with a notation that the section is not applicable.

It is not enough to submit an EU RMP summary as submitted for another jurisdiction. Your summary should contain Canadian-specific considerations.

Introduction

The introduction section should indicate that the document summarizes the content of the RMP.

Provide sufficient information to identify the product, including the:

- brand name of the product
- name of the market authorization holder
- submission control number

The following text template may be used:

> This is a summary of the risk management plan (RMP) for [product brand name] by [market authorization holder] under submission control number [submission control number]. The RMP describes important risks of [product name], [how these risks can be reduced or prevented] and how more information will be obtained about [product brand name]'s risks and uncertainties (missing information).
>
> [Product brand name]'s product monograph and its patient medication information give essential information to health care professionals and patients on how [product brand name] should be used.

The drug and what it is used for

In this section, in a paragraph provide the:

- name of the active substances
- approved indications of the drug in Canada
- route of administration of the product as reflected in the Canadian market authorization

Associated risks and minimization measures

Itemize routine risk minimization measures and state if the product has:

- routine or additional pharmacovigilance measures
- additional risk minimization measures
- missing information

List of important risks and missing information

In this section, provide a list of the:

- important identified risks
- important potential risks
- missing information

The list should contain all the important risks and missing information from the RMP, including Canadian-specific considerations.

The list should be presented in a table for easy reference.

Sample table for list of important risks and missing information

List of important risks and missing information

Classification	Details
Important identified risks	- - -
Important potential risks	- - -
Missing information	- - -

Summary of important risks

Provide a separate table for each important identified risk and important potential risk. In each table, provide a summary of:

- evidence for linking the risk to the drug
- risk factors and risk groups
- routine and additional risk minimization measures
- additional pharmacovigilance measures, if applicable

Provide a separate table for each missing information. In each table, provide a summary of:

- routine and additional risk minimization measures
- additional pharmacovigilance measures, if applicable

The summary of each important risk should contain information from the RMP, including Canadian-specific considerations.

Sample table for important identified risks and important potential risks

Important identified risk or important potential risk

Insert risk as indicated in List of important risks and missing information

Presentation of the risk	Details
Evidence for linking the risk to the drug	-
Risk factors and risk groups	-
Routine and additional risk minimization measures	-
Additional pharmacovigilance measures	-

Sample table for missing information

Missing information

Insert missing information as indicated in the List of important risks and missing information

Presentation of missing information	Details
Risk minimization measures	-
Additional pharmacovigilance measures	-

Definitions

The definitions and terminology consider documents prepared by Health Canada and other regulators, such as the European Medicines Agency (EMA).

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

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

Existing risk management plan: The most recent risk management plan that is provided to the Minister by a manufacturer and found to be acceptable.

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

"Important identified risks" are identified risks that are likely to impact the benefit-risk balance of the drug or have implications for public health. Important identified risks included in the RMP usually require measures to prevent, reduce or further characterize them.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH): A joint regulatory-industry initiative for the international harmonization of regulatory requirements for drugs. The parties in ICH represent the regulatory bodies and research-based industry in 3 regions: North America, Europe and Japan. Most new medicines are developed in these regions.

ICH E2E: An ICH guidance that helps plan pharmacovigilance activities, especially in preparation for the early post-marketing period of a new drug. It focuses primarily on specific aspects of a safety specification and pharmacovigilance plan that sponsors/MAHs may submit when they apply for market authorization.

Label: Includes any legend, word or mark attached to, included in, belonging to or accompanying any drug.

Medication error: Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care provider, patient or consumer. These may be related to professional practice, drug products, procedures and systems. They may also include errors in relation to:

- prescribing
- communicating orders
- product labelling, packaging and nomenclature
- compounding
- dispensing
- distribution
- administration
- education
- monitoring
- use

Missing information: Information on the safety of the drug that may:

- have a likely impact on its benefit-risk balance or
- have implications for public health
- be missing and needs to be collected and further characterized
- include gaps in knowledge about its safety
    - for example, gaps in particular patient populations or for certain anticipated uses

New active substance (NAS): A new drug (pharmaceutical or biologic) that:

- contains a medicinal ingredient not previously approved in a drug in Canada
- is not a variation of a previously approved medicinal ingredient

Note: "Approved" means for human or veterinary use.

Periodic Benefit-Risk Evaluation Report (PBRER): A pharmacovigilance document that provides a comprehensive, concise and critical analysis of new or emerging information on the risks of the drug and its benefit in approved indications. Health Canada uses the PBRER to appraise the drug's overall benefit-risk profile.

As per the updated ICH E2C(R2) guidance, Periodic Safety Update Reports (PSURs) for marketed drugs are used to evaluate safety, benefits and risks, as well as all relevant available information accessible to sponsors/MAHs.

Periodic Safety Update Report (PSUR): Sponsors/MAHs use the PSUR to summarize interval safety data and conduct a systematic overall safety evaluation on a regular basis. As well as covering ongoing safety issues, the PSUR includes updates on:

- emerging or urgent safety issues
- major signal detection and evaluation

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.

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.

"Important potential risks" are potential risks that if further characterized and confirmed would impact the risk-benefit balance of the drug or have implications for public health. Such risks included in the RMP would usually require further evaluation as part of the pharmacovigilance plan.

Reference RMP: A sponsor/MAH's company core RMP or EU-RMP that contains the essential elements of a risk management plan, which may be supplemented with a Canadian-specific addendum. This should not be confused with an RMP for a reference product used in a biosimilar or generic submission or application.

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.

Risk minimization tools (RMTs): Documents or materials used in the implementation of the additional risk minimization measures. Examples include:

- educational materials (such as health care professional guides or checklists, patient guides, patient cards)
- communications tools used in direct health care professional communications
- tools, documents and materials used in a pregnancy prevention program or a controlled access or distribution program

Safety specification: A detailed description of important identified risks, important potential risks and missing information relating to the safety of a drug. The safety specification should address:

- the populations potentially at risk (where the drug is likely to be used) and
- outstanding safety questions that warrant further investigation to refine understanding of the benefit-risk profile during the post-authorization period

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

Resources

Submission process and content

- Filing submissions electronically
- Guidance document: Product monograph
- Fees for the review of drug submissions and applications
- Guidance document for industry – Review of drug brand names
- Guidance document: Labelling of pharmaceutical drugs for human use
- Post-notice of compliance (NOC) changes: Safety and efficacy document
- Guidance for industry: Management of drug submissions and applications
- Preparation of drug regulatory activities in the common technical document (CTD) format

Pharmacovigilance and other practices and standards

- Reporting adverse reactions to marketed health products
- Good pharmacovigilance practices (GVP) guidelines (GUI-0102)
- Labelling requirements for non-prescription drugs guidance document
- Good label and package practices guide (GLPPG) for prescription drugs
- Draft guidance document – The use of foreign reviews by Health Canada
- Notifying Health Canada of foreign actions – Guidance document for industry
- Good label and package practices guide for non-prescription drugs and natural health products
- Guidance document – Submission and information requirements for extraordinary use new drugs (EUNDs)
- Preparing and submitting summary reports for marketed drugs and natural health products – Guidance document for industry
- Submission of targeted risk management plans and follow-up commitments for prescription opioid-containing products - Guidance for industry
- Notice: Adoption of the International Conference on Harmonisation (ICH) guidance on periodic benefit risk evaluation report – ICH topic E2C(R2)
- Notice: Implementation of risk management planning including the adoption of International Conference on Harmonisation (ICH) guidance Pharmacovigilance planning – ICH topic E2E

International Conference on Harmonization (ICH) guidance documents

Find the following guidance documents by accessing the International Conference on Harmonization (ICH) website:

- ICH E2C-R2: Periodic benefit-risk evaluation reports (PBRERs)
- ICH E2E: ICH harmonized tripartite guideline: Pharmacovigilance planning E2E

European Medicines Agency guidelines

Find the following guidelines by accessing the European Medicines Agency (EMA) website:

- Guidance on format of the risk management plan in the EU – in integrated format
- Guideline on good pharmacovigilance practices: Module V – Risk management systems

Contact us

Biologic and Radiopharmaceutical Drugs Directorate:

Office of Regulatory Affairs
Ground Floor, LCDC Bldg
Address Locator 0601C
100 Eglantine Dr
Ottawa ON K1A 0K9
Fax: 613-941-1708
Email: brdd.ora@hc-sc.gc.ca

Marketed Health Products Directorate:

Regulatory Project Management Office
Bureau of Strategic Engagement and Integrated Management Services
Health Canada
200 Eglantine Dr
Address Locator 1912A
Ottawa ON K1A 0K9
Email (biologics/radiopharmaceuticals): bbrs.rpm-gpr.bbra@hc-sc.gc.ca
Email (pharmaceuticals): mpb.rpm-gpr.bppc@hc-sc.gc.ca

Natural and Non-prescription Health Products Directorate:

Regulatory Project Manager
Non-prescription Drug Evaluation Division
Health Canada
2 Constellation Dr
Address Locator 2605A
Ottawa ON K2G 5J9
Email: nded-demvso@hc-sc.gc.ca

Pharmaceutical Drugs Directorate:

Regulatory Project Management Division
Pharmaceutical Drugs Directorate
Health Canada
1600 Scott St
Address Locator 3106B
Ottawa ON K1A 0K9
Email: rpmd-dgpr@hc-sc.gc.ca