Health Canada Santé Canada

Submitting risk management plans draft guidance document

This guidance document will replace the following guidance documents:

- *Guidance document - Submission of risk management plans and follow-up commitments*
- *Submission of targeted risk management plans and follow-up commitments for prescription opioid-containing products - Guidance for industry*

Canada

Forward

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 links included are a starting point to help sponsors/MAHs, and is not an exhaustive list of guidance documents.

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Introduction

Policy objectives

Health Canada has adopted and integrated the use of risk management plans (RMPs) and the International Conference on Harmonization (ICH) E2E Guideline into the regulatory review of drugs in Canada. This long-standing practice has now been incorporated into the *Food and Drug Regulations*. This will:

- support a life cycle approach to drug vigilance
- align drug vigilance with international best practices
- enhance the quality of Health Canada's regulatory assessments
- support Canadians' timely access to safe, efficacious and high quality drugs
- support ongoing evaluation of information that could have an impact on the benefit-risk profile 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 product, 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
- assesses the effectiveness of those risk minimization measures and interventions

Health Canada may require RMPs for drug products when the Minister has reasonable grounds to believe:

- there is a significant degree of uncertainty respecting 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, characterize, prevent or minimize risks or address uncertainties of that drug product
- assess the safety and effectiveness of the drug, for example, in deciding whether 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 document provides the sponsor/market authorization holder (MAH) with guidance on when and how to submit an RMP and RMP updates during the lifecycle of the drug product.

The document also provides clarification on:

- an acceptable RMP format
- RMP summaries and an acceptable RMP summary format
- requirements for taking into account the Canadian context, including the format for a Canadian-specific addendum
- RMP updates with Health Canada

Additionally, this document provides:

- clarification to the sponsor/MAH regarding the management of the submission of RMPs
- the sponsor/MAH with an overview of review timelines including deadlines for responding to questions
- the sponsor/MAH with information on compliance with other requirements related to RMPs

The regulatory requirements, principles and practices outlined in this document apply to "drugs," as defined by section 2 of the *Food and Drugs Act*, for human use and include the products within the scope of ICH E2E:

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

This document does not apply to the submission of RMPs for:

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

Readers of this document should be familiar with those requirements of the *Food and Drugs Act* and *Food and Drug Regulations* relating to routine pharmacovigilance measures such as adverse reaction reporting and summary reporting.

Please note that elements of RMPs, such as controlled 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 delay or hinder comparative testing with generic products or hinder their ability to enter the market.

Background

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

This decision is based on the information available at the time of authorization. The knowledge related to the safety profile of the drug can change over time through expanded use in terms of patient characteristics and the number of patients exposed. In particular, 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, Canada was a signatory to the ICH Pharmacovigilance planning E2E guideline, released in 2004. The ICH E2E guideline provides instruction in cases where there are "important identified risks of a drug, important potential risks, and important missing information, including the 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 ICH E2E Guideline, the European Medicines Agency (EMA) and other regulators have released their own guidelines to reflect the intent of the ICH E2E, and update them from time to time. Many sponsors/MAHs refer to EMA GVP Module V as their preferred approach.

In February 2009, Health Canada published the Notice regarding implementation of risk management planning. The notice advised on:

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

In June 2015, Health Canada published the Guidance document – Submission of risk management plans and follow-up commitments. This document provided sponsors/MAHs with guidance on how to proceed when submitting an RMP. The regulatory amendments to the *Food and Drug Regulations* build on long-standing practice outlined in the 2015 guidance document. In August 2020, Health Canada published a notice of clarification specifying that RMPs are not meant to restrict access to Canadian reference products. In November 2020, Health Canada published a second notice of clarification regarding the inclusion of Canadian-specific considerations in RMPs.

In response to the growing public health crisis due to opioids, the Minister of Health announced the Federal Action on Opioids on June 17, 2016. In November 2016, Health Canada convened a Scientific Advisory Panel on Opioids (SAP-Opioids) to provide recommendations on the monitoring and managing of the risks related to opioids. Recommendations from this panel were taken into consideration for the development of this guidance document.

Definitions

The definitions and terminology are derived from documents prepared by Heath Canada and other regulators such as the European Medicines Agency (EMA).

Additional measures:
additional pharmacovigilance measures and/or additional risk minimization measures.

Additional pharmacovigilance measures (also known as additional pharmacovigilance activities):
measures, activities or methods designed to address products with special safety concerns, not sufficiently addressed by routine pharmacovigilance measures, such as the need for additional data to more fully characterize risks or to evaluate the effectiveness of additional risk minimization measures. Examples include safety studies or registry.

Additional risk minimization measures (also known as additional risk minimization activities):
an intervention, in addition to the routine risk minimization measures, intended to prevent or reduce the probability of an undesirable outcome, or to reduce its severity should it occur. Examples include controlled distribution programs or educational material.

Compliant risk management plan:
a risk management plan that meets the requirements set out in section C.01.700 of the *Food and Drug Regulations*.

Core RMP:
a risk management plan, in an acceptable format, and which contains all of the essential elements of the EU format.

Data package:
a formal submission or application to a regulatory authority to obtain a regulatory decision or to maintain regulatory status for a drug. In Canada, this includes data as per the *Food and Drug Regulations* or other information filed for review by Health Canada. Examples include risk management plans filed independently of a submission, periodic safety update reports.

Foreign reviews (also referred to as foreign review reports):
scientific safety, efficacy and/or quality reports prepared by foreign regulatory authorities, upon which foreign regulatory decisions on drugs are based. They include initial scientific assessments, regulatory correspondence with the sponsor/MAH, follow-up assessments, and the final decision (for example, positive, negative or conditional). They include, where applicable, risk management plans and on-site evaluation reports (or equivalent). They do not include the data package filed with the foreign regulatory authority.

ICH E2E:
this ICH Guidance on Pharmacovigilance Planning 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 at the time of an application for market authorization.

Important identified risks:
undesirable clinical outcomes for which there is sufficient scientific evidence to show they are caused by the drug product, and which are likely to impact the benefit-risk balance of the product or have implications for public health. Important identified risks included in the RMP usually require measures to prevent, reduce or further characterize them.

Important potential risks:
risks that if further characterized and confirmed, would impact the risk-benefit balance of the product or have implications for public health. For example, where there is a scientific rationale that an adverse clinical outcome might be associated with off-label use, use in populations not studied or the long-term use of the product, the adverse reaction should be considered a potential risk and if deemed important, should be included in the list of safety concerns as an important potential risk. Important potential risks included in the RMP would usually require further evaluation as part of the pharmacovigilance plan.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH):
a joint regulatory-industry initiative pertaining to the international harmonization of regulatory requirements for drug products. 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.

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 healthcare professional, patient, or consumer. Medication incidents may be related to professional practice, drug products, procedures and systems, and include prescribing, order communication, product labelling/packaging/nomenclature, compounding, dispensing, distribution, administration, education, monitoring and use.

Missing information:
information on the safety of the drug product, likely to have an impact on its benefit-risk balance or have implications for public health, that is missing and needs to be collected. Such missing information may include gaps in knowledge about the safety of a drug product for certain anticipated uses (for example, long-term use) or in particular patient populations. The absence of data itself (for example, exclusion of a population from clinical studies) does not automatically constitute a safety concern. Instead, the risk management plan should focus on situations that might differ from the known safety profile. A scientific rationale is needed for the inclusion of that population as missing information in the RMP.

New active substance (NAS):
A new drug (pharmaceutical or biologic) that contains a medicinal ingredient not previously approved in a drug in Canada and that is not a variation of a previously approved medicinal ingredient. (*approved* means for human use or for veterinary use, as the case may be)

Opioid-related harms:
any adverse drug reaction related to opioid use disorder or opioid induced disorders as described in the *Diagnostic and Statistical Manual of Mental Disorders 5th edition* (DSM-5), resulting from therapeutic or non-therapeutic use of a drug product.

Periodic Benefit-Risk Evaluation Report (PBRER):
a pharmacovigilance document intended to provide a comprehensive, concise and critical analysis of new or emerging information on the risks of the drug product, and on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile. The updated ICH E2C(R2) guidance ensures that Periodic Safety Update Reports (PSURs) for marketed drugs have the role of being periodic benefit-risk evaluation reports by covering: safety evaluation, evaluation of all relevant available information accessible to sponsors/MAHs and benefit-risk evaluation.

Periodic Safety Update Report (PSUR):
a mechanism for summarizing interval safety data, and for conducting an overall safety evaluation. It is a tool for sponsors/MAHs to conduct systematic analyses of safety data on a regular basis. In addition to covering ongoing safety issues, the PSUR should also include updates on emerging and/or urgent safety issues, and major signal detection and evaluation that are addressed in other documents.

Pharmacovigilance:
the World Health Organization (WHO) defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse events or any other drug-related problems.

Post-Authorization Safety Study (PASS):
a study relating to an authorized drug product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the drug product, or of measuring the effectiveness of risk management measures. A PASS may be interventional or non-interventional.

Risk Evaluation and Mitigation Strategies (REMS):
Risk Evaluation and Mitigation Strategies (REMS) are required by the U.S. Food and Drug Administration from the sponsor/MAH to manage known or potential serious risks associated with a medicine to ensure that the benefits outweigh its risks. REMS use risk minimization strategies beyond labelling.

Risk Management Plan (RMP):
a document that describes a set of pharmacovigilance measures and interventions designed to identify, characterize, prevent or minimize risks and address uncertainties related to the safety and effectiveness of drug products, and the assessment of the effectiveness of those interventions (adapted from the EMA definition of a Risk Management System).

Risk Management Plan Summary (RMP Summary):
a document within the Risk Management Plan that reflects and summarizes the content of the Risk Management Plan.

Risk minimization measures (also known as risk minimization activities):
interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur. Examples include warnings in the label or minimization measures beyond routine, such as healthcare professional educational material.

Routine pharmacovigilance measures (also known as routine pharmacovigilance activities):
measures, activities or methods that are sufficient for post-approval safety monitoring of products for which no special concerns have arisen. Examples include monitoring of the safety profile of the product through signal detection activities and preparation of reports for regulatory authorities (for example, PSURs).

Routine risk minimization measures (also known as routine risk minimization activities):
standard measures or activities that apply to all drug products. Examples include product labelling and limitations on drug pack size.

Safety specification:
a detailed description of the important identified risks of a drug product, important potential risks and missing information. The safety specification should also address the populations potentially at risk (where the drug is likely to be used) and outstanding safety questions which 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 that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death.

List of relevant guidance documents and notices

Submission process

- Guidance for industry: Management of drug submissions and applications
- Guidance document: Preparation of drug regulatory activities in the Electronic Common Technical document format
- Guidance document: Creation of the Canadian Module 1 Backbone
- Canadian Module 1 Schema Version 2.2
- Preparation of drug regulatory activities in the Common Technical Document (CTD) format
- Guidance document: Product monograph
- Product monograph master template
- Fees for the review of drug submissions and applications
- Guidance document for industry - Review of drug brand names
- Post-Notice of Compliance (NOC) changes: Safety and efficacy document
- Regulatory enrolment process (REP)

Vigilance practices and standards

- Notice: Implementation of risk management planning including the adoption of International Conference on Harmonisation (ICH) guidance Pharmacovigilance planning - ICH Topic E2E
- Reporting adverse reactions to marketed health products
- Notifying Health Canada of foreign actions - Guidance document for industry
- Notice: Adoption of the International Conference on Harmonisation (ICH) guidance on periodic benefit risk evaluation report - ICH Topic E2C(R2)
- Draft guidance document – The use of foreign reviews by Health Canada
- 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
- Good pharmacovigilance practices (GVP) guidelines (GUI-0102)
- Good label and package practices guide (GLPPG) for prescription drugs
- Good label and package practices guide for non-prescription drugs and natural health products
- Labelling requirements for non-prescription drugs guidance document

International Conference on Harmonization (ICH) guidance documents

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

European Medicines Agency guidelines

- Guideline on good pharmacovigilance practices: Module V – Risk management systems
- Guidance on format of the Risk Management Plan (Plan) in the EU – in integrated format

United States Food and Drug Administration guidance

- Format and content of a risk evaluation and mitigation strategy (REMS) document – Guidance for industry (draft)
- Risk evaluation and mitigation strategies: Modifications and revisions; Guidance for industry
- Survey methodologies to assess REMS goals that relate to knowledge guidance for industry

Procedures to submit

When to file a risk management plan with Health Canada

As required by the *Food and Drug Regulations*, sponsors/MAHs **must** submit RMPs to Health Canada if:

- there is a **significant degree of uncertainty** respecting 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

A sponsor/MAH must submit an RMP:

- as part of a new drug submission (NDS), abbreviated new drug submission (ANDS), extraordinary use new drug submission (EUNDS) or abbreviated extraordinary use new drug submission (AEUNDS) when required or upon request from Health Canada
- upon request from Health Canada following the submission of an application seeking a drug identification number (DIN)
- as part of a supplemental new drug submission (SNDS) when a new RMP or an RMP update is required to assess the safety and effectiveness of the drug in relation to the matters that are the subject of the SNDS
- when requested by Health Canada post-authorization
- when an update is required due to significant differences in risks or uncertainties, or to the measures the sponsor/MAH intends to take, as described in the existing plan

Here are some further explanations and some examples of when to file an RMP with Health Canada.

As part of a drug submission or application

Examples of when to file an RMP with Health Canada include:

- new drug submissions that include new active substances (NAS)
- generic and biosimilar drugs whose reference product has an RMP with additional measures
- drug products where one of the components of a drug-drug kit has a separate DIN with an RMP that includes additional measures

Sponsors/MAHs must also include an RMP in a drug submission seeking issuance of a notice of compliance (NOC) for drugs with the designation "extraordinary use".

The RMP assists the Minister in assessing the safety and effectiveness of the drug as part of drug submissions.

Health Canada may also require, in writing, an RMP following the submission of an application for a DIN where:

- there is a significant degree of uncertainty respecting 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

Health Canada may consider that there is a **significant degree of uncertainty** respecting the risks associated with the drug when:

- there are significant outstanding uncertainties regarding the safety and effectiveness of the drug that cannot be resolved based on the data reviewed to grant market authorization of the product
    - For example, this could be in the form of missing information for particular populations, or for anticipated uses, such as long-term use or specific populations, not studied prior to the drug submission application. There may also be missing information related to the use of a drug product, such as in situations where the clinical trials supporting the market authorization included a small number of patients.
    - Missing information (such as, exclusion of a population from clinical studies) does not always constitute a safety concern. A scientific rationale is needed to determine whether exclusion of that population is missing information for the purposes of an RMP.

- the anticipated use of the drug includes settings that differ from clinical trials, such as in a larger population when there are concerns about its use in those larger settings or the drug is expected to be highly used in a population with additional risk factors compared to the studied population.
- An RMP may be required to identify and further characterize the uncertainties to prevent or mitigate risks associated with such uncertainties.
- 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.
- risks have either been identified or there are potential risks associated with the drug, but more information is required to characterize those risks and their impact on the safety and effectiveness of the drug
    - Examples of risks or uncertainties that may not be fully characterized could include the potential for off-label use, long-term use or use in patients with comorbidities. An RMP may be required due to the uncertainty surrounding these risks to further study, characterize and manage the risks.
- a product produced by innovative technologies may merit greater scrutiny than one that is made using established, well-characterized ones
    - Examples could include certain gene therapies or cell therapies.

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:

- the risk would not only be serious, but may have an impact on the balance of benefits and risks of the product
    - An RMP may be required when a serious risk has already been identified and characterized and where additional measures or interventions may need to be either considered, or required, to prevent or minimize the risk.
    - An RMP may also be required to provide an assessment and evaluation of the effectiveness of any additional measures or interventions proposed.
    - Examples could include relevant risks identified from reports of adverse reactions in clinical trials, epidemiological studies and so on, including issues emerging from post-market use (for example, off-label use, medication errors).
- the drug is a member of a class of drugs with known safety concerns and uncertainties for which additional measures may already be in place
    - Additional risk minimization measures could include physician or patient educational materials, restricted access and so on.
    - An example could include products known to present opioid-related harms.

For a discussion of "serious risk", refer to annex A of the Amendments to the Food and Drugs Act: Guide to new authorities.

If sponsors/MAHs have questions about whether they are required to submit an RMP to Health Canada, we encourage them to begin communicating early with the Regulatory Project Management Office of the Marketed Health Products Directorate. They should do this well in advance of their application or the submission process.

Generic and biosimilar drugs

An example of when to file an RMP with Health Canada is a generic or biosimilar drug whose reference product has an RMP with additional measures, such as:

- certain types of designated laboratory tests
- restricted distribution programs
- distribution of educational materials, patient alert cards
- post-market safety studies
- registries

Sponsors of a generic or biosimilar drug should consider the risk profile in comparison to the reference product and consider additional measures, such as risk minimization measures and pharmacovigilance measures, accordingly.

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

Sponsors/MAHs of generic and biosimilar drugs are encouraged to review posted RMP summaries of the reference product, when available, to determine whether the innovator product has additional measures in advance of the submission process. If a posted RMP summary is not available, sponsors/MAHs of generic and biosimilar drugs should refer to the Drug Product Database or the Canadian Product Monograph to identify if additional measures have been implemented for the reference product.

If sponsors/MAHs have questions regarding the need for additional measures, we encourage them to contact the Regulatory Project Management Office at the Marketed Health Products Directorate (MHPD).

The sponsor/MAH, as part of their RMP, would be expected to consider the need of similar additional measures for their product, and describe those measures as appropriate. If the additional measures in the generic or biosimilar RMP differ from the reference product RMP, the sponsor/MAH should provide a rationale.

Not as part of a drug submission or application

Health Canada may **also** require an RMP not linked to a drug submission or application when no RMP has been submitted to Health Canada in the past.

The decision to exercise this requirement would be made on a product-by-product basis, depending on information available at the time. Such a request may be part of an ongoing review to support informed regulatory decision making about the drug, including to assess its safety and effectiveness.

Health Canada may request an RMP for drugs that have already been assigned a DIN, when the Minister has reasonable grounds to believe that there is a **significant degree of uncertainty** respecting the risks associated with the drug.

- A drug associated with actions subsequent to authorization, such as cancellation of a DIN, discontinuation of sale, suspension of an NOC or stop sale, may also be subject to a request for an RMP either at the point of market re-entry or subsequently, especially if the action was associated with a serious safety issue or significant uncertainty.
- An RMP may be required when an emerging serious safety issue of significant potential risk is confirmed from a signal that requires further characterization to identify how the risk will impact the safety and effectiveness of the drug
- For example, a major new safety concern found in a product from the same class.

Health Canada may also request an RMP for drugs that have already been assigned a DIN, when the Minister has reasonable grounds to believe 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.

- An RMP may be required when an emergent serious risk has been identified and where additional measures or interventions may be required to prevent or minimize the risk. This could occur when a serious safety signal or a significant change, in what is known about the risks of the drug, is identified through an Annual Summary Report, Periodic Safety Update Report (PSUR) or Periodic Benefit-Risk Evaluation Report (PBRER) or report of a foreign regulatory action.

The time frame for RMP submissions that are not part of a drug submission or drug application would be established by Health Canada after discussion with the sponsor/MAH. In general, a 30-day timeline is sufficient for most RMP requests. If the sponsor/MAH fails to provide the RMP within the time specified and an extension has not been provided or the request has not been withdrawn, the sponsor/MAH must not sell the drug until an RMP compliant with section C.01.700 of the *Food and Drug Regulations* has been provided.

Updates on what is meant by "significantly different"

Sponsors/MAHs are required to 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 relating to those risks, are **significantly different** from those that are described in the existing plan.

When the risks and uncertainties are significantly different, the existing RMP may no longer be sufficient to meet its purpose of identifying, characterizing, preventing or minimizing the risks or addressing uncertainties of the drug.

Examples of risks and uncertainties being significantly different include:

- a new or heightened risk or uncertainty
- a new or expanded target population, for example as a result of a new indication
- increased potential for medication error or accidental exposure

Examples of how these may be identified include:

- an annual summary report under section C.01.018 of the *Food and Drug Regulations*
- an assessment ordered under section 21.31 of the *Food and Drugs Act*
- an issue-related summary report under section C.01.019 of the *Food and Drug Regulations*
- a foreign regulatory action (for example, reported under section C.01.050 of the *Food and Drug Regulations*)

An RMP update is also required when the measures that the sponsor/MAH intends to take to address and monitor the uncertainties relating to the drug's risks or to prevent or reduce those risks are significantly different than those that are described in the existing plan, including:

- new additional measures
- the removal of additional measures
- the significant alteration of additional measures
- changes to the evaluation of the effectiveness of the additional measures in Canada

You can find more information on risk management plan updates further on this page, including examples of a significant difference.

The following changes are not considered significant:

- changes made to an RMP in a foreign jurisdiction relate to an indication not authorized in Canada
- changes that do not relate to the conditions of use outlined in the Canadian product monograph, or the risks, uncertainties or additional measures described in the existing RMP submitted to Health Canada

However, if the changes made to an RMP in a foreign jurisdiction relate to the safety specification or the additional measures that are applicable to Canada or previously included in the RMP submitted to Health Canada, the sponsor/MAH must assess:

- whether the detailed description of the risks in the RMP is still sufficient
- if the pharmacovigilance plan is still sufficient to address and monitor the uncertainties related to risks associated with the drug
- if the risk management plan is still sufficient to prevent or reduce the risks associated with the drug

An updated RMP must be provided if the results of the assessment show a significant difference to the safety specification or the additional measures.

If sponsors/MAHs have questions regarding whether there is a significant difference in information, or whether they are required to submit an updated RMP to Health Canada, we encourage them to contact the Regulatory Project Management Office at MHPD.

Health Canada may require an updated RMP from the sponsor/MAH when the Minister has reasonable grounds to believe that

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

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

- controlled distribution programs
- educational tools or materials
- risk communications
- prescriber checklists
- patient wallet cards
- pregnancy prevention programs
- patient testing and monitoring

Generally, such updates to an RMP would be required by the Minister when the existing RMP is no longer sufficient to identify, characterize, prevent or minimize the risks or address uncertainties of the drug, or to assess the safety and effectiveness of the drug.

Supplemental New Drug Submission

When submitting a supplemental new drug submission (SNDS) or a supplemental abbreviated new drug submission (SANDS), an RMP or an RMP update may be needed to assess the safety or effectiveness of the drug when the risks or uncertainties are significantly different from those contained in the new drug submission or abbreviated new drug submission.

For example, an RMP or an RMP update may be requested, in writing, when an SNDS (or SANDS) is submitted for any of the following matters:

- the labels used in connection with the new drug
- the packages of the new drug
- the representations made with regard to the new drug respecting
    - the recommended route of administration of the new drug
    - the dosage of the new drug
    - the claims made for the new drug, including changes in indication
    - the contra-indications and side effects of the new drug
    - the withdrawal period of the new drug
- the dosage form in which it is proposed that the new drug be sold

Some examples for an SNDS (or SANDS) when an RMP or RMP update may be required include:

- there is a change in indication or the extension of an existing indication to a vulnerable population
- there are new conditions of use (for example, from administration by a health care professional to self-administration in the home setting, or vice-versa)

For requests made following an SNDS (or SANDS) to assess the safety and effectiveness of the drug in relation to the matters that are the subject of the SNDS (or SANDS), the applicable timelines apply.

Acceptable risk management plan format

All RMPs submitted to Health Canada must meet the requirements established in section C.01.700 of the *Food and Drug Regulations*. Health Canada will determine if the RMP submitted is a compliant RMP under the *Regulations*.

To meet the requirements of the *Food and Drug Regulations*, a compliant RMP must take into account the Canadian context and must include the following:

- product overview
    - a description of the drug and what it is used for
- safety specification
    - a detailed description of the risks and uncertainties of the drug (important identified risks, important potential risks and missing information)
- pharmacovigilance plan
    - a detailed description of the measures the sponsor/MAH intends to take to address and monitor the uncertainties (routine pharmacovigilance measures and additional pharmacovigilance measures)

- risk minimization measures
    - a detailed description of the measures that the sponsor/MAH intends to take to prevent or reduce the risks (routine risk minimization measures and additional risk minimization measures)
- evaluation of the effectiveness of risk minimization measures
    - a detailed description of how the sponsor/MAH intends to evaluate the effectiveness of the measures that the sponsor/MAH intends to take to prevent or reduce the risks
- summary of the RMP
    - a summary of the plan's contents, in English and in French

Health Canada will accept RMPs in the following acceptable formats to meet the requirements of a compliant RMP:

- the EU format
- other formats if they include all the required elements outlined above

A compliant RMP must take into account the Canadian context. Where warranted, sponsors/MAHs must include a Canadian-specific addendum containing information specific to the Canadian context, unless the sponsor/MAH has prepared the RMP specifically for Canada and has taken into account the Canadian context throughout the Canadian RMP.

General considerations

An RMP reflects safety data that is both clinical and non-clinical. It should be updated throughout the drug's life cycle as discussed and agreed upon with Health Canada and the sponsors/MAHs. When submitting RMPs, Health Canada encourages sponsors/MAHs to:

- submit one RMP per brand name product (not per indication)
- submit the most recent version of the RMP available
- notify Health Canada if a revised RMP becomes available later during the regulatory review process
- provide a foreign RMP review and an attestation form (if available)
- include available post-market data if marketed in Canada or elsewhere
- For example, if there is a submission in Canada for a drug that is already marketed elsewhere (for example, Europe), there will be value in including the market experience of that drug in the RMP.
- examine the potential for new or heightened safety concerns for combination drugs relative to the individual products
- provide a rationale, supported by scientific evidence, for the change, addition or removal of any safety concern, additional pharmacovigilance measure or additional risk minimization measures from the previous RMP version submitted to Health Canada
    - If referencing changes that have been implemented or planned in another jurisdiction/country, provide the evidence to support such a change and an evaluation of any relevant Canadian data that supports a similar change in Canada.
- submit both clean and track change versions of the RMP and addendum to the RMP (if revised) and clearly outline the major changes made since the last version was submitted to Health Canada
- provide a rationale in situations where additional pharmacovigilance measures (for example, a drug utilization study, registry) or risk minimization measures (for example, contraindication, restricted distribution, educational material) are proposed or implemented in major jurisdictions (for example, Europe or the U.S.) but not in Canada
- This information can be included in an appendix to the RMP or Canadian addendum.
- reference the most recent version of the Canadian product monograph
- refer to EMA's Guidance on the format of the risk management plan (RMP) in the EU - in integrated format

For more information on submission requirements, refer to:

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

Sponsors/MAHs should have an adequate system in place to manage RMPs. An adequate system should:

- adapt to scientific and technical progress throughout the lifetime of the drug
- include proper documentation of all measures taken
- ensure that all persons involved in the procedures and processes of the quality systems be appropriately qualified and trained
- include in any subcontracts a description of the process in place to ensure third parties are in compliance with the subcontracted pharmacovigilance measures

For more information on adequacy of a pharmacovigilance system refer to:

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

Submission

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, refer to:

- Guidance document: Preparation of drug regulatory activities in the Electronic Common Technical Document format

For submissions in 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 general procedures on how to file submissions, refer to:

- Guidance document: Management of drug submissions and applications

Use of foreign reviews

Sponsors/MAHs should provide reviews from regulatory authorities in the U.S. (FDA) and from the EU's centralized procedure (EMA) if they are available at the time of initial submission of the data package. For RMPs attached to a submission, if the foreign RMP review is not available at the time of initial submission but becomes available later during the regulatory review period, sponsors/MAHs can submit it as "unsolicited information."

Health Canada may also consider reviews from other foreign regulatory authorities.

In situations where more than 1 foreign review is available, submit all that are available.

For more information on the use of foreign reviews, refer to:

- Draft guidance document: The use of foreign reviews by Health Canada

Cover letter and note to reviewer

A cover letter and a note to reviewer should accompany all RMPs, updates and other related documents to reviewers. If the RMP is included with a submission, the cover letter should reference the RMP.

The cover letter should indicate:

- the submission type, for example, RMP update
- information requested by Health Canada, if any
- whether the submission relates to an existing RMP

The note to reviewer can refer to:

- if an RMP update, a clear outline of the changes that have been made subsequent to the previous submission
- scientific information related to the reason for submission
- unsolicited information, which can include:
    - new safety concerns identified by the sponsor/MAH
    - proposed changes to existing risk minimization or pharmacovigilance measures
- other (please specify)

For more information on the cover letter and the note to reviewer, refer to:

- Guidance document: Preparation of drug regulatory activities in the Electronic Common Technical Document format

How to prepare a Canadian-specific addendum

A Canadian-specific addendum is not required if the RMP has been prepared specifically for Canada, using an acceptable RMP format, and has taken into account the Canadian context throughout the Canadian RMP.

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

Examples of special considerations for the Canadian context and related to medical practice or populations in Canada when submitting an RMP or related documents include:

- information related to Canadian patient exposure
- genetic or extrinsic factors that are specific to the Canadian population
- the epidemiology of the medical condition(s) or risk factors that reflect the authorized indication(s) in Canada
    - for example, Canadian epidemiology data such as incidence rate and prevalence in Canada for the proposed indicated population
- post-authorization experience in Canada and worldwide
    - for example, if a drug has been marketed outside of Canada for a period of time, there would be knowledge about emerging risks not identified in clinical trials (sponsors/MAHs should submit a summary of this information to Health Canada)
- important public health issues specific to Canada and specific measures needed to address, monitor, reduce or prevent them
    - for example, opioid-related harms

The Canadian-specific addendum should also include:

- RMP submission history in Canada
- safety issues specific to Canada
- pharmacovigilance measures in the Canadian context/setting
    - this could involve monitoring Canadian adverse events from sponsor/MAH's database and reconciliation of such event(s) with adverse reactions in Health Canada's Canada Vigilance Database
- risk minimization measures and evaluation of their effectiveness in the Canadian context/setting
- appropriate milestones and timelines for reporting on additional pharmacovigilance and risk minimization measures that are applicable to Canada

Find more information on preparing a Canadian-specific addendum.

RMP summaries

Sponsors/MAHs must submit an RMP summary as part of their submission, including for RMP updates, as part of the requirements under section C.01.700. The summary should be written in plain language, and must be submitted

in both English and French. The plain language should be clear and concise and should be accessible for a wide audience, including:

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

The format of the RMP summary should mirror the EU RMP summary format and include all the following essential elements:

- an overview of the drug and what it is used for
- a summary of the risks and how they are managed
- a summary of any missing safety information to be collected
- any additional measures, including:
    - additional risk minimization measures
    - additional pharmacovigilance measures
- a list of planned studies to provide more information on the safety of the drug

The RMP summary must include Canadian-specific considerations and reflect and summarize the content of the Core RMP. The Canadian-specific considerations can either be included:

- throughout the summary
- in a Canadian-specific section included within the RMP summary

Health Canada will consider the RMP summary as part of the overall RMP review. The sponsor/MAH is expected to incorporate proposed changes to the RMP into the RMP summary during the course of the review.

To support transparency and to increase access to information on drugs, Health Canada intends on publishing RMP summaries, in both official languages, in a publicly accessible web location and format. As such, it is the sponsor/MAH's responsibility to verify that the RMP summary contains no confidential business information that they do not want made public.

Find more information on preparing an RMP summary.

Risk management plan updates

An RMP update is required when:

- requested by Health Canada when, on the basis of new information obtained after the existing plan was provided to the Minister, the Minister has reasonable grounds to believe that:
    - the risks associated with the drug, or the uncertainties relating to those risks, are significantly different than those that are described in the existing plan
    - the drug presents a serious risk of injury to human health that warrants measures to reduce the probability or severity of such an injury that are significantly different than those described in the existing plan

- the MAH concludes that what is known about the risks or uncertainties associated with the drug is significantly different than when the drug was authorized or when the existing plan was submitted:
    - the risk management measures are modified after the sponsor/MAH learns about new information that may lead to a significant difference in the risks or uncertainties of a drug in the Canadian context, for example:
        - identification of serious safety concerns which require additional pharmacovigilance measures or changes to the risk minimization measures
        - significant changes to the Safety Specification section due to the addition of new evidence (quantitative or qualitative) related to risks or uncertainties concerning opioid-related harms or other risks and uncertainties generated through risk-monitoring/characterizing activities conducted in Canada or internationally to investigate the drug
    - the final study results confirm a safety risk that requires changes to various parts of the RMP
    - the summary of safety concerns changes, including when another regulator such as the EMA has approved the addition, removal or reclassification of safety concerns
- the measures that the MAH intends to take are significantly different than the existing RMP, previously submitted to Health Canada, including:
    - an additional pharmacovigilance or risk minimization measure is ceased, added or substantially altered
    - any changes to the objectives, population or due date of final results for any of the studies listed in the RMP

The sponsor/MAH must provide the RMP update as soon as feasible, or if the update has been requested by Health Canada, within the time specified in the request.

If the sponsor/MAH fails to provide an updated RMP when requested by Health Canada, within the time specified, and an extension has not been provided or the request has not been withdrawn, the sponsor/MAH must not sell the drug until a compliant updated RMP has been provided.

Sponsors/MAHs of generic and biosimilar drugs are encouraged to review posted RMP summaries of the reference product, when available, to determine whether the reference product has made significant updates to their RMP. An updated generic or biosimilar product RMP may be required, as appropriate.

Each RMP update should have a distinct version number and date. When sponsors/MAHs revise any part of the RMP:

- a new RMP version number should be assigned each time
- the revision date should be reflected as the "last revised" date, which is when the RMP is considered final

Review of risk management plans

Review bureaus at the MHPD conduct the review of RMPs, updates and other related document. Review bureaus include the:

- Bureau of Biologics, Radiopharmaceuticals and Self-Care Products (BBRS)
- Marketed Pharmaceuticals Bureau (MPB)
- Office of Policy, Risk Advisory and Advertising (OPRAA)

The RMP review time may vary from product to product. If the RMP is part of a submission, the applicable timelines for those submissions apply.

Pre-submission meetings for RMPs that are intended to be part of a drug submission

Sponsors wishing to file a submission with Health Canada are encouraged to determine whether an RMP is required. If needed, sponsors can also request a pre-submission meeting to discuss all aspects of their submission including RMPs.

When an RMP is required, or if requested by Health Canada prior to submission, the RMP must be included with the submission package in accordance with the relevant submission requirements.

Sponsors should:

- refer to the Guidance document: Management of drug submissions and applications for instructions on how to request pre-submission meetings
- request their pre-submission meeting, if needed, and indicate in the request that the sponsor will have discussion points related to the RMP, if applicable

During a pre-submission meeting, MHPD representatives will aim to provide appropriate guidance on the content and format of the RMP, based on the information provided in the meeting package. Sponsors may include a draft RMP in the data package for a pre-submission meeting. Alternatively, sponsors may provide an outline of the RMP or any potential questions related to the RMP.

Correspondence, screening and review of RMPs that are part of a drug submission

Regulatory correspondence for RMPs attached to a submission should include reference to the control number.

Health Canada will screen the submission. If the sponsor/MAH does not provide an RMP for a product where one is required, Health Canada will request one.

After Health Canada considers the submission acceptable to enter review, the RMP will be forwarded to the MHPD. The MHPD conducts the RMP review in parallel with the review of other submission components by the pre-market bureaus.

Health Canada may communicate with the sponsor to clarify RMP-related issues during the review. Health Canada may also share with the sponsor:

- comments stemming from the RMP review
- the RMP review report, upon request

Review of RMPs not included in a submission

This process describes how Health Canada manages RMPs not included in a submission.

Health Canada may send a letter to the sponsor/MAH at any time, requiring an RMP or an update to an existing RMP.

Examples of RMPs submitted to Health Canada outside of a drug submission can include:

- an RMP update for a Canadian marketed drug for which a new emerging or serious post-market safety issue is identified
- an RMP for a Canadian marketed drug for which there are significant uncertainties relating to the risks associated with the product
- an RMP update for a Canadian marketed drug for which a new serious safety risk is identified for a similar product in the class
- an RMP update when measures included in the existing RMP are no longer sufficient to identify, characterize, prevent or minimize risks or address uncertainties of that drug

The MHPD may communicate with the sponsor/MAH to clarify RMP-related issues during the review. Sponsor/MAHs should send responses to these clarification requests to the attention of the MHPD. The MHPD will communicate with the sponsor/MAH on the compliance of the document or on deficiencies identified by the MHPD.

If the MHPD has identified deficiencies in the RMP, it sends a feedback letter to the sponsor/MAH including the timelines for response. The timeline to respond should be between 15 to 30 calendar days. These are guidelines and can be adjusted due to the nature of the request.

Health Canada will share the RMP review report with the sponsor/MAH upon request.

Compliance and implementation

Health Canada will communicate with the sponsor/MAH to confirm the compliance of the RMP following review. For an RMP to be compliant, it must meet the requirements of section C.01.700 of the *Food and Drug Regulations*.

As part of the review, Health Canada will evaluate the RMP based on the requirements in the *Food and Drug Regulations*, and will make a determination on compliance based on the:

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

The compliance of the RMP will also take into consideration whether the plan, including the proposed measures are feasible and reasonable.

When an RMP is required as part of a submission, Health Canada will consider the RMP in making its decision regarding the issuance of the market authorization. As such, if the RMP is non-compliant with the regulations or deficient, this has an impact on the authorization decision.

Sponsors/MAHs are expected to implement and perform the pharmacovigilance and risk minimization measures in accordance with the descriptions and timelines detailed in the compliant RMP. They are also expected to implement and perform any agreed-upon measures detailed in subsequent compliant RMP updates.

Health Canada may request follow-up actions from the sponsor/MAH, as needed.

Health Canada may impose Terms and Conditions on a product's DIN in relation to an element or measure related to, or within, the RMP. Namely, terms and conditions may be imposed where they are **necessary** to ensure the management of risks and resolution of uncertainties. Examples could include:

- the required implementation of a specific pharmacovigilance or risk minimization measure
- a requirement to submit significant milestones outlined as reportable outcomes regarding a pharmacovigilance or risk minimization measure

For more information on Terms and Conditions, refer to:

- Draft guidance document on terms and conditions (T&Cs) for human and veterinary drugs

Contact information for submitting an RMP or other related documents

Sponsors/MAHs 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, please consult the following guidance documents:

- 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, please consult the following guidance documents:

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

Status requests

In an effort to streamline administrative processes and expedite drug submission reviews:

- senior regulatory affairs officers are assigned to each submission in BRDD
- regulatory project managers are assigned to each review bureau in PDD, NNHPD and MHPD

The regulatory project managers and officers will serve as the primary points of contact between the review bureaus and the sponsor/MAH.

Sponsors/MAHs with questions regarding the RMP component of their submissions should contact the regulatory project manager in MHPD.

Record-keeping requirements

Sponsors/MAHs should retain a copy of the compliant RMP and maintain records of the decisions they made in the creation of the plan, together with the information relied on in making those decisions.

All decisions relating to creating or updating the RMP should be documented, including the decisions made relating to:

- 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 the sponsor/MAH may rely on when making 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 the sponsor/MAH intends to take, as well as the manner in which they intend to evaluate the effectiveness of those measures. As such the sponsor/MAH should also maintain the following:

- documentation supporting the implementation and operation of the RMP
- effectiveness of the measures outlined in the RMP
- materials that support additional pharmacovigilance 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

Where other regulatory requirements for document retention do not apply, Health Canada recommends the sponsor/MAH retain the RMP and the records for at least:

- 5 years following the submission of an updated RMP **or**
- 5 years following discontinuation of the drug in Canada, if an updated RMP has not been submitted

The sponsor/MAH is also responsible for preserving data integrity. Based on how documents are preserved, the sponsor/MAH 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, sponsors/MAHs are encouraged to review the following:

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

RMP summary template

Summary specifications

The RMP summary should include specific sections, which mirror the EU RMP Summary format sections. These are:

- an introductory paragraph
- 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

In the event that 1 or more of the sections do not apply, they should still be included in the RMP summary with a notation that the section is not applicable.

It is insufficient to submit an EU RMP summary as submitted for another jurisdiction. This is because the summary must contain Canadian-specific considerations and must be provided in both English and French.

For a template of the EU RMP summary, refer to:

- Guidance on the format of the risk management plan (RMP) in the EU – in integrated format

Introductory paragraph

The introductory paragraph should indicate the purpose of the document and the name of the product.

It is suggested that the following text template be used, which is the text template used in the EU RMP template, modified for Canada:

"This is a summary of the risk management plan (RMP) for [*product name*]. The RMP details important risks of [*product name*], [*how these risks can be reduced or prevented*] and how more information will be obtained about [*product name*]'s risks and uncertainties (missing information).

[*Product name*]'s product monograph and its patient medication information give essential information to health care professionals and patients on how [*product name*] should be used."

The drug and what it is used for

In this section, provide in paragraph form the:

- name of the active substances
- approved indication(s) 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 format for ease of reference.

Sample table for list of important risks and missing information

List of important risks and missing information	
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
- risk minimization measures
- additional pharmacovigilance measures, if applicable

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

- risk minimization measures
- additional pharmacovigilance measures, if applicable

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

1006 Sample table for important identified risks important potential risks

Important identified risk or important potential risk **Insert risk as indicated in List of important risks and missing information**	
Evidence for linking the risk to the drug	
Risk factors and risk groups	
Risk minimization measures	Routine and additional measures
Additional pharmacovigilance measures	

1007 Sample table for missing information

Missing information **Insert missing information as indicated in List of important risks and missing information**	
Risk minimization measures	
Additional pharmacovigilance measures	

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Canadian-specific addendum template

What to include in a Canadian-specific addendum

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
- RMP submission history in Canada
- safety specification
- pharmacovigilance measures in Canada
- risk minimization measures and evaluation of their effectiveness in Canada
- summary or conclusion of the RMP in Canada
- references
- appendices

In the event that 1 or more of the sections do not apply, such section(s) should still be included in the Canadian-specific addendum with a notation that the section is not applicable.

Cover page

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

- "risk management plan Canadian-specific addendum for [*name of product or proposed brand name*]"
- proper name or non-proprietary name in final dosage form
- the date of submission
- version, date of final sign-off and data lock point for the current Canadian-specific addendum
- version, date of final sign-off and data lock point for the core RMP

RMP submission history in Canada

In this section, provide the versions, in chronological order, of the RMPs submitted to Health Canada for evaluation, including a summary of changes made for each version. Include versions submitted by previous DIN holders, if applicable. This information can be in a table format for ease of reference, and should include:

- the core RMP version
- the Canadian-specific addendum version
- the date the RMP was submitted to Health Canada
- the application number (DSTS control number)
- a summary of changes from the previous version to the Canadian-specific addendum, or core RMP from the previous version submitted to Health Canada
- the rationale for change
- a scientific rationale should accompany significant changes to the RMP or Canadian-specific addendum

Core RMP version (for example, EU-RMP v1.0)	Canadian-specific addendum version (for example, CSA v1.1)	Date submitted (yyyy-mm-dd)	Application number (DSTS control number) (for example, RMP update submission # 123456)	Summary of changes from previous versions (for example, changed MACE from important potential risk to important identified risk)	Rationale for change (for example, new study results)

Safety specification

In this section, provide:

- the Canadian epidemiology
- a summary of Canadian-specific safety concerns
- a summary of any proposed changes

Epidemiology of the indications and target populations relevant to Canada

Indication

Provide the current or proposed indication 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). Specify any notable differences from the core 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 U.S.
- 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:

- the targeted population for use of the product, including specified groups such as:
    - age or age categories such as pediatric or geriatric
    - sex or gender
    - racialized and/or ethnic minorities (when relevant for assessment of safety and risk management)
    - underrepresented and/or underserved populations, such as:
        - pregnant or lactating people
        - patients with psychiatric disorders
        - patients with relevant comorbidities
        - populations with specific religious constraints
- the intended prescriber for the product and any considerations related to the medication use process, from prescribing to dispensing to administration and monitoring of the product
- the setting in which the product 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 yearly and cumulative patient exposure in Canada since product launch.

Canadian-specific safety concerns

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

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

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

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

It's not sufficient evidence to cite acceptance of such a change by another regulator without providing a rationale as justification.

If additional safety concerns need to be considered or a risk is reclassified or removed, provide a description and the scientific rationale for the changes. For the Canadian context, examples include:

- genetic, external or other factors that are unique to the population, such as:
    - 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
- post-authorization experience worldwide and in Canada, including regulatory actions since product approval (Canadian and worldwide)
    - include reference to the section in the core RMP

Sample summary table of safety concerns in Canada

Summary of sponsor's safety concerns

Safety concern	In Core RMP	In 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 that all pharmacovigilance measures, including routine measures and additional measures, listed in the core RMP apply to Canada. If the pharmacovigilance measures are not relevant to the Canadian context, provide an explanation.

Routine pharmacovigilance measures in Canada

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

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

If these routine pharmacovigilance measures in Canada differ from the core RMP, provide an explanation.

If there are Canada-specific safety concerns identified in the previous section, describe the routine pharmacovigilance measures that have been, or will be, implemented to address these safety concerns.

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

Additional pharmacovigilance measures in Canada

Provide information on the additional pharmacovigilance measures in the Canadian context, such as copies of the study protocols or synopsis.

For each additional pharmacovigilance measure listed in the core 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

Where additional pharmacovigilance measures only apply to Canada or if international pharmacovigilance measures differ from those proposed for Canada, provide a description and a detailed reason for these differences.

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

If there are Canadian-specific additional pharmacovigilance measures that are not listed in the core RMP, provide a detailed description of the additional pharmacovigilance measures using the same format as in the core 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 that all risk minimization measures, including routine measures and additional measures listed in the core RMP apply to Canada. If the risk minimization measures do not apply to Canada, provide an explanation.

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. If these routine risk minimization measures in Canada differ from the core RMP, provide an explanation.

When discussing routine risk minimization measures in Canada, refer to the most recent version of the Canadian product monograph, product packaging and product labels.

Additional risk minimization measures in Canada

Provide information on the additional risk minimization measures in the Canadian context, including a history of additional risk minimization measures that may have been discontinued.

For these measures:

- include the objective and rationale
- include a description of 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 plans 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 are different, explain the reason for these differences

Include in the appendix copies of any tools or materials used in risk minimization measures.

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, restricted access 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			

Summary of the RMP in Canada

In this section, provide a summary of the:

- safety issues specific to Canada
- routine and additional pharmacovigilance measures
- risk minimization measures

Sample summary table of risk management information

Safety concern May refer to core RMP if concerns are the same	Pharmacovigilance measures (routine and additional)	Risk minimization measures (routine and additional)
Important identified risks		
Important potential risks		
Missing information		

References and appendices

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 in Canada
- additional risk minimization materials used in Canada, such as:
    - consent forms
    - patient/caregiver guide
    - patient cards, wallet/alert cards
    - health care professional checklist
    - health care professional education program/materials

Opioid products

Objective for opioid products

Opioid products need to include specific content within their RMP to address:

- the risk and uncertainties of opioid-related harms in Canada
- other risks and uncertainties posed by the product, where warranted

The objective of establishing Canadian-specific content for RMPs for opioid products is to:

- standardize and strengthen the rigour of the post-market surveillance of prescription opioids
- better quantify and characterize the risks associated with opioid-related harms in Canadian patients
- put targeted risk minimization measures in place to prevent or decrease prescription opioid-related harms in Canada

Sponsors/MAHs are encouraged to work together, where possible, to develop a common approach for pharmacovigilance studies and for risk minimization measures for opioids that share the same active ingredient or therapeutic use or indication. This would support consistency among the various measures and minimize duplication.

When developing an RMP for an opioid product, the sponsor/MAH should seek early dialogue with Health Canada's Marketed Health Products Directorate regarding the applicability, feasibility and design of the proposed measures.

Canadian opioid-specific content for compliant RMPs

Specific content related to opioid harms and uncertainties was previously included in the Canadian Specific Opioid targeted Risk Management Plan (CSO-tRMP) for Class B opioids, which was required as a term and condition. RMP requirements for opioids are now subsumed under the RMP regulations.

In order for an RMP for an opioid product to address opioid-related harms in Canada, Canadian-specific elements should be included in:

- a core RMP **or**
- the Canadian-specific addendum

This is part of the Canadian context, which must be taken into account in the RMP. It is insufficient to leverage only international data and measures to fulfil these requirements for opioid-related harms in Canada.

Opioid-specific content should be included in addition to the standard RMP elements described in this guidance document, and in other referenced acceptable formats (such as the EU), when preparing an RMP for an opioid product. Health Canada expects that the content of the opioid RMP will cover:

- opioid-related harms within the detailed description of the risks associated with the drug and the uncertainties related to those risks
- other important risks and missing information associated with the opioid drug in Canada

The update requirements of an RMP for opioids are as specified elsewhere in this guidance document.

Safety specification

Include the following Canadian opioid-specific content within the safety specification of the RMP prepared for the opioid product:

- the Canadian epidemiology of the indication and trends of opioid-related harms in Canada
- a description, quantitatively and qualitatively, of the occurrence of opioid-related risks associated with the use of the opioid drug in Canada
- detailed information on the evidence gaps and uncertainties related to opioid-related risks that are associated with the use of the opioid drug in Canada
- an analysis and characterization of opioid-related harms and other important safety concerns
- a summary table of safety concerns and proposed changes

Epidemiology of the indications and the target populations in Canada

Provide a breakdown, according to the formulation, regarding opioid-related harms collected from active surveillance (such as a completed post-authorization safety study) when:

- discussing the epidemiology of the indications and target populations **and**
- when more than 1 formulation is covered in the same opioid RMP (for example, ER/IR)

Include the Canadian trends of opioid-related harms relevant to the product, relating to, for example:

- region
- indication
- time
- age, sex or gender
- concomitant use of other substances known to interact with opioids
- underrepresented or marginalized populations

Post-authorization experience

When discussing the post-authorization experience, provide an analysis of opioid-related harms based on both crude numbers and reporting/incidence rates of events in the context of worldwide and Canadian post-market exposure (if applicable).

Update this information as new quantitative or qualitative evidence related to opioid-related harms or uncertainties is generated through the risk-monitoring/characterizing measures conducted in Canada or internationally. These measures may include pharmacoepidemiological studies or clinical trials undertaken to investigate the drug.

Pharmacovigilance measures

Include the following Canadian opioid-specific content within the pharmacovigilance measures of the RMP prepared for the opioid product:

- routine (passive surveillance) and additional (active surveillance) measures in place or to be put in place to monitor and characterize risks and uncertainties associated with the use of the drug in Canada
- the timelines for conducting the activities and reporting
- a summary table of pharmacovigilance measures and milestones

Routine pharmacovigilance measures

When discussing the Canadian-specific monitoring of adverse events for routine pharmacovigilance measures for opioid products, clearly document:

- a search strategy (including the data lock point)
- the most recent Adverse Reaction Terms (MedDRA Preferred Terms) used for spontaneous data extraction

Additional pharmacovigilance measures

Because of well-recognized limitations related to adverse reaction reporting, passive adverse event surveillance alone is insufficient to monitor opioid-related harms in Canada. An RMP for an opioid product should describe additional pharmacovigilance measures to monitor opioid-related harms and address current knowledge gaps in Canada. Examples of these measures include:

- a retrospective non-interventional post-authorization safety study (PASS) in high-risk populations
- a well-designed prospective non-interventional PASS estimating the incidence of opioid–related harms in the indicated patient population
- a surveillance system capable of monitoring (longitudinal or cross-sectional), opioid-related harms discussed associated outcomes, among diverse populations in Canada

Prepare study protocols before initiating studies, with input from qualified methodologists and statisticians. Make the choice of risk factors beforehand, and with the anticipated direction of effect to reduce the risk of spurious findings. Include factors that have already been established by the literature. When possible present significant associations for risk factors as both relative and absolute effects.

The sponsor/MAH's role should be restricted to:

- sponsoring
- reviewing of the protocol
- provision of non-binding feedback

Do not let parties that stand to benefit financially from the results unduly influence study design, implementation or interpretation. Non-profit organizations should conduct post-marketing studies.

Submit pharmacovigilance measure progress reports either in a follow-up report or in an updated RMP.

Risk minimization measures in Canada and evaluation of their effectiveness

Include the following Canadian opioid-specific content within the risk minimization measures of the RMP prepared for the opioid product:

- a description of routine and additional risk minimization measures (beyond the approved product label) that are designed to reduce or prevent:
    - the occurrence of opioid–related risks
    - other product-specific risks in people in Canada using the drug
- the timelines for conducting the activities and reporting
- all materials that are or will be communicated and/or disseminated by the MAH to healthcare professionals with respect to the drug
- a summary table of risk minimization measures and their evaluation

Additional risk minimization measures

An RMP for an opioid product should describe additional risk minimization measures designed to reduce or prevent the occurrence of opioid-related harms in people in Canada using the drug.

For additional risk minimization measures, it is recognized that the risk minimization approach may evolve throughout the therapeutic product life cycle and a variety of tools could be implemented in the future. Moreover, this approach may be required for some products depending on their unique benefit/risk profile. Such additional measures could include, for example:

- implementation of restricted access
- establishment of performance-linked access programs/registries as defined by CIOMS IX

When assessing whether the proposed measures prevent or reduce the opioid related risks, Health Canada will consider:

- the added positive effects of the product's benefit-risk balance
- unintended consequences on the existing workflow and standard of care in various health care settings

Include in the appendix copies of any tools or materials used in risk minimization measures.

Evaluation of the effectiveness of the risk minimization measures

The sponsor/MAH is expected to provide a detailed section on the evaluation of the effectiveness of risk minimization measures for Canadian opioid-specific content that:

- describes the measures that the manufacturer will carry out to assess the effectiveness of the risk minimization measures on health outcomes in Canadians who are using the opioid product
- provides the timelines for the conducting of the activities

Overall, the strategies to assess the effectiveness of the risk minimization aim to determine whether:

- the risk minimization measures achieve the desired level of risk management
    - objective (quantifiable) measures that aim to determine this success are considered as outcome indicators
- the risk minimization has been successfully implemented
    - objective (quantifiable) measures that aim to evaluate the success of the implementation of these measure are considered as process indicators

Since the ultimate goal of a risk minimization measure is to reduce or prevent risks, the sponsor/MAH must provide outcome indicators.

Acceptable examples of outcome indicators include:

- frequencies or rates of opioid-related harms (before and after implementing risk minimization)
- any metrics related to changes in hospitalizations or deaths related to opioid-related harms (before and after implementing risk minimization)

Evaluating the effectiveness of risk minimization generally uses:

- drug utilization studies
- prescriber and patient surveys
- surveillance studies of key safety outcomes

Examples of opioid products that require Canadian opioid-specific content within their RMP

The following list of products are examples of opioid products for which the Minister has required RMPs with specific content. The *Food and Drug Regulations* give the Minister the authority to require RMPs for any drug that meets the thresholds prescribed in the regulations.

Drugs intended for human use containing any of the following active ingredients	Including (but not limited to)	Qualifier
Buprenorphine	Buprenorphine Hydrochloride	n/a
Butorphanol	Butorphanol Tartrate	n/a
Codeine	Codeine Phosphate	Except for those products referred to in subsection 36(1) of the *Narcotic Control Regulations*
Diamorphine	Diamorphine Hydrochloride; Diacetylmorphine Hydrochloride	n/a
Fentanyl	Fentanyl Citrate	n/a
Hydrocodone	Hydrocodone Bitartrate	n/a
Hydromorphone	Hydromorphone Hydrochloride	n/a
Meperidine	Meperidine Hydrochloride	n/a
Methadone	Methadone Hydrochloride	n/a
Morphine	Morphine Hydrochloride; Morphine Sulfate	n/a
Normethadone	Normethadone Hydrochloride	n/a
Opium	Opium and Belladonna	n/a
Oxycodone	Oxycodone Hydrochloride	n/a

Drugs intended for human use containing any of the following active ingredients	Including (but not limited to)	Qualifier
Oxymorphone	Oxymorphone Hydrochloride	n/a
Pentazocine	Pentazocine Hydrochloride; Pentazocine Lactate	n/a
Tapentadol	Tapentadol Hydrochloride	n/a
Tramadol	Tramadol Hydrochloride	n/a

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