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

Health Canada Santé Canada

Canada

Health Canada is the federal department responsible for helping the people of Canada maintain and improve their health. Health Canada is committed to improving the lives of all of Canada's people and to making this country's population among the healthiest in the world as measured by longevity, lifestyle and effective use of the public health care system.

Également disponible en français sous le titre : *Ligne directrice sur la préparation et la présentation des rapports de synthèse pour les drogues et les produits de santé naturels commercialisés*

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Foreword

Guidance documents provide assistance to industry and healthcare 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 may be acceptable provided they are 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 other applicable guidance documents.

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Overview

Scope and application

This guidance document helps market authorization holders (MAHs) and licence holders prepare and submit annual summary reports for drugs and natural health products, interim summary reports for Natural Health Products or issue-related summary reports for drugs that comply with the following:

- Food and Drugs Act (FDA)
- Food and Drug Regulations (FDR) **or**
- Natural Health Products Regulations (NHPR)

An **annual summary report (ASR)** is a comprehensive assessment of all known safety information for a marketed drug or natural health product (NHP). It provides an update on the worldwide safety profile at defined intervals throughout the post-authorization life cycle of the drug or NHP.

An **interim summary report (ISR)** is a concise and critical analysis of specified safety information for an NHP since the date of the most recent annual summary report.

An **issue-related summary report (IRSR)** is prepared upon Health Canada's request and contains a concise, critical analysis of a specific safety or effectiveness issue concerning a marketed drug, based on an analysis of adverse reaction reports.

The principles and practices outlined in this guidance document apply to the following products for human use:

- pharmaceutical drugs
    - includes prescription and non-prescription drugs
- biologics as set out in Schedule D to the act
    - includes biotechnology products, vaccines and fractionated blood products

- radiopharmaceutical drugs as set out in Schedule C to the act
    - excludes positron-emitting radiopharmaceuticals used in a study
- natural health products (NHPs) as defined in Section 1 of the NHPR
- combination products (drug and device)

Blood and blood components, cells, tissues and organs, biocides and sperm and ova are beyond the scope of this guidance.

Note: ASRs submitted as data to support independent processes such as a market entry submission or application, or to support a **supplement** to a submission (for example a change to labelling, packaging or indication) are out of the scope of this guidance document. For more information on supporting data for a submission or application, consult:

- Guidance on management of drug submissions and applications
- Guidance Document: Post-Notice of Compliance (NOC) Changes: Safety and Efficacy Document (for pharmaceutical, biologic and radiopharmaceutical drugs for human use only)
- Natural Health Products Management of Applications Policy

Objectives

This guidance document provides:

- clarity on the expected content and format of ASR, ISR and IRSR
- an overview of the submission of such reports, including procedures for submitting to Health Canada
- clarity concerning the notification, without delay, of significant changes

Background

According to the World Health Organization (WHO), pharmacovigilance is "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem". This activity takes place throughout the lifecycle of a product, which is before, during and after marketing.

Health Canada expects industry to follow good vigilance practices (GVP), and we monitor compliance. An integrated approach that includes multiple information sources; documented and validated processes; and timely reporting to Health Canada is critical.

Responsibility for the safety of marketed drugs and NHPs in Canada is shared. MAHs and licence holders are responsible for the safety of their products throughout their life cycle and must comply with all Canadian legislative and regulatory requirements. Health Canada is responsible for enforcing Canadian legislative and regulatory requirements and monitoring risks associated with marketed products.

In addition to Canadian legislative and regulatory requirements, Health Canada aligns with international best practices wherever possible. As an official member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), we are committed to adopting and implementing ICH guidance such as ICH E2C(R2) Periodic risk-benefit report.

Preparing annual summary reports under the FDR

About annual summary report preparation requirements

In accordance with section C.01.018 of the Food and Drug Regulations (FDR), market authorization holders (MAHs) must prepare an annual summary report (ASR) of all information relating to adverse drug reactions and serious adverse drug reactions that they received or became aware of during the previous 12 months.

The annual summary report contains a concise, critical analysis of those reactions.

The requirement to prepare an ASR arises on the date that you first sell the product in Canada and continues throughout the product's life cycle.

In preparing the report, you must determine, based on the analysis, whether there has been a significant change in what is known about the drug's benefits and risks.

You must notify the Minister in writing without delay if you have not already done so, if in preparing the report you conclude that there has been a significant change.

Visit Definitions for an explanation of "sell" and of "significant change".

Preparing annual summary reports

You must meet all regulatory requirements of the FDR. Section C.01.018 includes a requirement to prepare and complete the report annually, and C.01.020 requires you to maintain the ASR for at least 25 years after the day on which it was created. You should also maintain documents used to prepare the ASR, to assist with compliance verification.

Preparing the report consists of collecting, analyzing and organizing the relevant data about adverse drug reactions and serious adverse drug reactions, including contextual information, that enables you to determine whether there has been a significant change in the risk-benefit profile. The preparation of the report is an ongoing activity throughout the reporting period linked to signal management processes and monitoring activities.

Continuous and periodic signal management processes and monitoring activities, such as environmental scanning, are important for the preparation of an ASR.

It's essential that manufacturers and regulatory authorities have the most up-to-date information on a drug. A concise, critical analysis must be rigorous enough to identify any significant changes in the risk-benefit profile. The timing, frequency and nature of monitoring activities for signal detection depend on a number of factors, such as:

- the product's risk profile
- known or specific emerging issues
- volume of adverse drug reaction reports received
- scheduled timing or preparation of the summary report

Identified and potential safety issues, as well as knowledge gaps (for example, toxicity in vulnerable sub-populations, interactions with other products, emergent use patterns) may require more active monitoring.

In addition to reviewing your internal databases and information, you are advised to review the Canada Vigilance Adverse Reaction online database for information relevant to the preparation of your ASR. For more information on scanning the database and your obligations concerning serious adverse drug reaction reporting, consult:

- Clarification of section 4.3 of the Reporting adverse reactions to marketed health products guidance: Notice

You are encouraged to use terminology from the Medical Dictionary for Regulatory Activities (MedDRA) to analyze and present data.

You may choose the 12-month period for which the ASR is prepared as long as there are no gaps between reporting periods. For example, you may choose to shift the 12-month period to align with your commitments in other jurisdictions, as long as there is no gap between the date on which you first sell your product and the ASR reporting periods. We prefer that ASRs be prepared with harmonized data lock points (DLPs) based on the international birth date (IBD) of the active substance. If you are unable to identify the IBD, refer to the EU reference dates (EURD) list.

The report must be prepared on an annual basis, regardless of timeline requirements in other jurisdictions. Common practice is to complete the report within 70 calendar days of the data lock point, as outlined by ICH E2C(R2) for an annual report, unless our request letter for the submission of an ASR specifies a different timeline.

ASRs are not expected to discuss problems related to quality or good manufacturing practices, unless they result in adverse clinical outcomes. Good manufacturing practices (GMP)-related safety issues should be distinguished from ingredient-related safety issues.

Note: There may be instances when the MAH chooses to contract another party to carry out certain activities on behalf of the MAH. These activities could include maintaining records related to adverse reaction data or conducting pharmacovigilance activities, including preparing or submitting ASRs.

For more information, consult:

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

Visit Definitions for an explanation of "vulnerable sub-populations".

Although ASRs must be prepared annually, they are **only** to be submitted:

- upon our request
- to fulfill a term or condition imposed by the Minister under the Food and Drug Regulations

Visit Submitting annual reports for information on when to submit.

Content of an annual summary report

The information you include in the ASR will depend on the adverse reaction data received or known to you. If you cannot complete a section (for example because you have not become aware of any adverse reactions within a reporting period), note this and provide an explanation.

Adverse reaction reports as well as other sources of information that might be necessary for the analysis should be considered. Other data sources may include:

- foreign regulatory websites
- reports of medication errors (including incidents without clinical consequences such as near misses and reports of concern)
- public information, such as social media or media reports of side effects

You should include in your concise critical analysis, where available, information on emergent safety issues, whether domestic or foreign. Examples of such information include:

- findings from clinical studies
- actions on comparable products from foreign regulators or other MAHs
- new and significant safety findings published in peer-reviewed scientific and medical literature or made available as unpublished manuscripts, on the product or suspect ingredient(s)

Collecting this information is part of your ongoing routine pharmacovigilance and signal detection.

An ASR should add to what is known about the product's safety from real-world use. Available reference safety information, for example, product monographs, core company data sheets or core company safety information (referred to as "global reference safety information") should be part of your assessment. If your product has a Canadian risk management plan (RMP), the summary of safety concerns should also be part of your assessment.

Even for products with well-established safety profiles, safety issues may emerge. The depth of analysis needed for the ASR depends on the nature and amount of the information collected. ASRs summarize and integrate new cumulative safety knowledge gained from experience during the reporting period.

At minimum, your concise critical analysis should address the following, where relevant:

- whether there is a need to take action or if action has been taken (for example, for safety reasons) during the reporting interval by MAH or foreign competent authorities
- changes to reference safety information during the reporting interval
- separate global and Canadian exposure (interval/cumulative) in
    - related clinical trials
    - post-marketing
- summary of significant safety findings from clinical (interventional and non-interventional) studies during the reporting interval
- summary of medication errors during the reporting interval, including incidents without clinical consequences
- summary of significant safety findings from non-clinical studies during the reporting interval, if applicable
- summary of significant findings from a literature search covering the reporting interval
- summary of reports of unusual failure in efficacy or lack of effectiveness during the reporting interval
- opened, ongoing and closed safety signals during the reporting interval

- summary of new safety information identified during the reporting interval, including new information for each safety concern in the Canadian RMP for:
    - important identified risks
    - important potential risks
    - missing information
- summary of new information arising from each additional pharmacovigilance activity in the Canadian RMP during the reporting interval
- evaluation of effectiveness of the risk minimization measures in the Canadian RMP during the reporting interval
- changes to the Canadian RMP implemented during the reporting interval or changes in-progress
- a discussion on misuse, off-label use, and deliberate or inadvertent exposures or intentional overdose
- conclusions on whether there has been a significant change in what is known about the risks and benefits during the reporting interval
- new safety information about the class of drugs in which the current drug is included, where evidence also exists that the safety concern also involves the current drug

Conclusions about a significant change

In preparing your ASR, you must include your conclusions on whether there has been a significant change in what is known about the risks and benefits of the drug during the period covered by the report. We expect you to determine whether there has been a change in the balance of the benefits and risks that would warrant urgent action. These conclusions are based on your concise critical analysis of the evidence, including an evaluation of the safety findings.

Not all safety findings or changes to the known risks and benefits of a drug are considered significant. You should note safety findings and changes and assess whether they meet the threshold of significant change.

Conclusions about a significant change could arise from information involving authorized or off-label use and may identify urgent action needed to:

- modify labelling or Canadian product monograph to include serious, boxed warnings and precautions or contraindications
- change in packaging to modify the dosing device
- communicate risks to public or health professionals
- update or add additional risk minimization measures, such as educational materials, pregnancy prevention program or controlled distribution or access

The focus of the assessment should be on the clinical significance of such a change, for example:

- the potential for significant morbidity or mortality
- the impact on patient quality of life or public health
- whether the change may alter clinical practice

The MAH's conclusion of a significant change should be made from the perspective of a reasonable person with objective knowledge of credible facts, sufficient experience or training and an understanding that the benefits of a marketed product must outweigh its risks.

For information on qualified personnel, consult:

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

The discovery of a significant change could have an impact on other vigilance activities and requirements. For example, a need to update your risk management plan (RMP), including measures that you intend to take.

For new drugs, you should also consider if the significant change represents a significant difference from material contained in the new drug submission (as described in s. C.08.003 (1) of the FDR) for which you are considering a supplement to a submission.

For more information on risk management plans and supplements to a submission, consult:

- Submitting risk management plans guidance document
- Guidance on management of drug submissions and applications

If, in preparing the ASR, you have concluded that there was a significant change and have already notified Health Canada without delay, you should document within the report the date and the means of notification.

Visit Definitions for an explanation of "significant change".

Acceptable document formats

You may prepare an ASR using one of the following standardized document formats:

- Periodic benefit-risk evaluation report (PBRER) format
    - preferred international format for drug summary safety reporting
    - follow the standards defined in the ICH E2C (R2) guidance (PDF)
- Periodic safety update report (PSUR) format
    - EU format and comparable to the PBRER format

You may also prepare an ASR using a non-standardized format, as long as it respects the expected content outlined in this guidance.

The format you choose will depend on the nature of the product and your preference. **However, you are encouraged to use the PBRER format**. The PBRER format helps manufacturers:

- prepare a comprehensive, cumulative, concise and critical analysis of new or emerging information on the risks and benefits of their products throughout their life cycle
- evaluate a product's overall benefit-risk profile

If our request letter specifies a preferred format, such as PBRER or PSUR, you should prepare the ASR in the format requested, where possible.

You may use two consecutive 6-month summary reports prepared for another regulatory authority to meet the regulatory requirements.

Canadian-specific information

Although standardized periodic summary reports such as PBRERs and PSURs are used globally, regional differences may exist. You should consider the need for a Canadian-specific section or addendum when preparing an ASR.

A concise critical analysis of Canadian-specific data should include, where relevant:

- adverse drug reactions occurring in Canada
- when there is no existing RMP in Canada, information such as the epidemiology of the medical condition or risk factors that reflect the authorized indication in Canada in cases where it varies from the authorized indication in other jurisdictions
- date of first marketing and current marketing status in Canada
- information on Canadian patient exposure
- interval post-marketing experience in Canada
    - updated information on safety concerns outlined in the Canadian RMP
    - updated information on pharmacovigilance activities in Canada, including summary of new information
    - information on risk minimization strategies, implementation of risk minimization measures outlined in the RMP, and evaluation of effectiveness of risk minimization activities in Canada
- specific analyses requested by Health Canada
- conclusions about significant changes

Note that the concise critical analysis should include both global and Canadian-specific information and should address the impact of any conclusions on the safety of the product in Canada, including:

- actions that have been taken in Canada for safety reasons during the reporting interval, for example, changes to reference safety information, such as the Canadian Product Monograph or Canadian labelling
- actions intended to be taken in Canada for safety reasons

If actions taken or intended to be taken in Canada differ from those taken in the foreign jurisdiction, a rationale should be provided.

Where applicable, the analysis should refer to:

- RMPs
- terms and conditions
- approved product labelling
- Canadian product monograph (CPM)

This section can be prepared as a Canadian-specific summary report or as an addendum to an already prepared summary report. This section can be prepared as a Canadian-specific summary report or as an addendum to an already prepared summary report, ensuring that the Canadian-specific information is annualized to meet the regulatory requirements, if the report is for a period greater than one year.

Notification of significant change

The regulations require that you notify the Minister in writing without delay, if, in preparing the ASR, you conclude that there has been a significant change in what is known about the risks and benefits of the drug during the period covered by the report.

The conclusion of a significant change depends on the available evidence and can occur at any time while the report is being prepared. The ASR does not need to be finalized for you to conclude that there has been a significant change and the requirement to notify without delay to be triggered. This can occur at any time during the annual cycle. However, the significant change must also be noted in the completed report.

To avoid overburdening the system, do not submit a notification of significant change unless it meets the threshold outlined in the definition of significant change.

Visit Definitions for an explanation of "significant change".

Issues related to the quality of the product or GMP are not in scope of this requirement and should not be notified in this manner.

Contact us if you have questions about notification of a significant change.

How to notify

The notification of a significant change must be made without delay, be clear and explicit, and must contain a description of:

- the significant change, including the emerging safety issue
- the basis on which the conclusion was made

You are also encouraged to include in your notification the following:

- clinical impacts of the issue on patient or public health, or impact on the product's benefit-risk profile
- what further assessments may be needed in the Canadian context
- follow-up actions needed in Canada with proposed timelines, if applicable, including:
    - enhanced or novel pharmacovigilance measures or risk minimization measures
    - changes to packaging, labelling, product design or product accessibility
    - risk communication

Note: You are expected to proceed with any intended actions outlined in your notification.

To notify us of a significant change, complete the form:

- Notifying Health Canada of a significant change in what is known about the risks and benefits of a product

The form is available upon request by emailing no-reply.MHPD.publications.DPSC.non-reponse@hc-sc.gc.ca. To receive the form automatically, the subject line must be exactly "Notifying Health Canada of a significant change form". Do not modify the subject line, as this may prevent the form from being delivered automatically.

Once complete, submit the form without delay in an electronic common technical document (eCTD) or non-eCTD format via the electronic submissions gateway (ESG) using the regulatory enrolment process (REP). A cover letter or note to reviewer is not required with your notification.

For information on how to prepare transactions in eCTD or non-eCTD format, consult:

- Filing submissions electronically

Contact us if you have questions about your submission.

It is not sufficient to provide an ASR instead of a notification of a significant change. You should not submit the ASR with your notification of significant change. If we need to assess the safety and effectiveness of the drug further to the significant change, we will request the ASR in writing.

If you have already notified us of a significant change, you do not need to notify us again, unless there is new information that represents another significant change.

If the significant change is identified as a consequence of receiving or becoming aware of information regarding a foreign action subject to the reporting requirements under C.01.050 of the Food and Drug Regulations, you may satisfy both requirements by notifying us without delay using the form:

- Notifying Health Canada of foreign actions in respect of a serious risk of injury to human health (safety signal or toxicity, adverse reactions, unsafe use)

The form is available upon request by emailing no-reply.MHPD.publications.DPSC.non-reponse@hc-sc.gc.ca. Ensure that only the exact text “Notifying Health Canada of foreign actions form” is in the subject line of the email.

Consult:

- Guidance on notifying Health Canada of foreign actions
- Submitting risk management plans guidance document
- Guidance to market authorization holders on issuing health product risk communications

- Guidance document: Post-notice of compliance (NOC) changes: Safety and efficacy document (for pharmaceutical, biologic and radiopharmaceutical drugs for human use only)

Discontinued products

After a product is discontinued in Canada, you should still prepare an ASR and report significant changes until the expiry date of the last lot sold.

Some adverse reactions and associated safety signals may appear soon after treatment starts, while others may take longer to appear. For example:

- Late reactions that occur rarely or not at all at the beginning of treatment, but whose incidence increases with continued or repeated exposure.
- Delayed reactions become apparent some time after a drug is used, even if the drug is withdrawn before the reaction appears.

Late and delayed adverse reactions can be due to carcinogenesis, development of drug tolerance and physical dependence or chronic organ damage caused by, for example, pulmonary fibrosis.

Well-known historical examples are:

- corticosteroids and osteoporotic fractures
- pergolide and cardiac valve fibrosis
- females exposed to diethylstilbestrol (DES) in utero developing lower genital tract cancers

Visit Definitions for an explanation of "discontinued".

Note: "Dormant" products, or products not actively being sold, are subject to the requirements until and unless they are discontinued or their DIN cancelled.

Preparing annual summary reports under the NHPR

About NHP annual summary report preparation requirements

Licence holders must prepare and maintain a summary report on an annual basis. This is in accordance with section 24(2) of the Natural Health Products Regulations (NHPR).

The annual summary report (ASR) contains a concise and critical analysis of all domestic adverse reactions and foreign serious unexpected adverse reactions to a natural health product (NHP) reported over the previous 12 months.

The requirement to prepare an ASR begins on the date that the product is first sold in Canada and continues throughout the product's life cycle.

Preparing NHP annual summary reports

You must meet all regulatory requirements of the NHPR. This includes annually preparing and maintaining the ASR.

Preparing the report consists of collecting, analyzing and organizing the relevant data about adverse reactions and serious adverse reactions, including contextual information, that enables you to determine whether there has been a significant change to the risk-benefit profile. The preparation of the report is an ongoing activity linked to signal management processes and monitoring activities.

Continuous and periodic signal management processes and monitoring activities, such as environmental scanning, are both important parts of routine pharmacovigilance and signal detection for the preparation of an ASR.

It's essential that licence holders and regulatory authorities have the most up-to-date information on an NHP. Your concise, critical analysis must be rigorous enough to detect any significant changes in the risk-benefit profile. The timing, frequency and nature of monitoring activities for signal detection depend on a number of factors, such as:

- the product's risk profile
- known or specific emerging issues
- scheduled timing or preparation of the summary report

Identified and potential safety issues, as well as knowledge gaps (for example, toxicity in vulnerable sub-populations, interactions with other products, emergent use patterns) may require more active monitoring.

In addition to reviewing your internal databases and information, you are advised to review the Canada Vigilance Adverse Reaction online database for information relevant to the preparation of your ASR. For more information on scanning the database and your obligations concerning serious adverse reaction reporting, consult:

- Clarification of section 4.3 of the Reporting adverse reactions to marketed health products guidance: Notice

For information on reporting adverse reactions to Health Canada, consult:

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

You are encouraged to use terminology from the Medical Dictionary for Regulatory Activities (MedDRA) to analyze and present data.

You may choose the 12-month period for which the ASR is prepared as long as there are no gaps between reporting periods. We prefer that ASRs be prepared as a cumulative summary from the date of first sale in Canada. The ASR should be prepared within 70 calendar days of the end of the most recent 12-month period.

Note: There may be instances when the licence holder contracts another party to carry out certain activities on their behalf. Examples of activities are maintaining records on adverse reaction data, conducting vigilance activities or preparing and submitting ASRs. The license holder is responsible for complying with regulatory requirements for their products. Regardless of whether or not this is done on their behalf by another party, these activities should be managed, performed and documented in a way that supports accountability and continuous improvement.

Visit Definitions for an explanation of "significant change" and "vulnerable sub-populations".

Content of NHP annual summary report

The information you include in the ASR will vary depending on the adverse reaction data received or known to you. If you cannot complete a section (for example because you

have not become aware of any adverse reactions within a reporting period), note this and provide an explanation.

Adverse reaction reports as well as other sources of information that might be necessary for the analysis should be considered. Other data sources may include:

- foreign regulatory websites
- consumer complaints of side effects
- reports of medication errors (including incidents without clinical consequences and reports of concern)
- public information, such as social media or media reports of side effects
- international or Canadian poison centre data (where available and accessible)
- safety findings published in peer-reviewed scientific and medical literature on the product or suspect active ingredient(s)

You should include in your concise critical analysis information on emerging safety issues related to your product or its ingredients. Collecting this information is part of your ongoing monitoring activities for signal detection.

An ASR should add to what is known about the product's safety from real-world use. Available reference safety information (such as product and ingredient monographs, approved product labelling or terms of market authorization) should also be assessed in the ASR as part of the analysis.

Safety issues may arise even for products with well-established safety profiles. The depth of analysis needed for an ASR depends on the nature and amount of the information collected. ASRs summarize and integrate new safety knowledge gained from experience during the reporting period.

At minimum, your concise critical analysis should discuss the following, where relevant:

- whether there is a need to take action or if action has been taken for safety reasons during the reporting interval by the licence holder or foreign competent authorities
- changes to reference safety information during the reporting interval
    - include copy of current reference safety information (such as company core safety information)

- global and Canadian exposure (interval/cumulative)
- summary of significant safety findings during the reporting interval
- summary of medication errors, including incidents without clinical consequences
- a discussion on misuse or overuse, and off-label use during the reporting interval
- opened, ongoing and closed safety signals during the reporting interval
- summary of new safety information identified during the reporting interval
- conclusions on whether there has been a significant change in what is known about the risks and benefits during the reporting interval

Canadian-specific information, where relevant, should be included in the ASR or in a Canadian-specific section or addendum, including:

- product packaging/inner and outer labels
- Canadian exposure
- Reference safety information (e.g. core company safety information)
- regulatory contact information in Canada
- date of first marketing and current marketing status in Canada

Conclusions about a significant change

In preparing your ASR, you should include your conclusions on whether there has been a significant change in what is known about the risks and benefits of the NHP during the period covered by the report. As such, you should determine whether there has been a change in the balance of the benefits and risks that would warrant urgent action. These conclusions would be based on your concise critical analysis.

Not all changes to risks and benefits are considered significant. You should note changes and assess if they meet the threshold of significant change.

The conclusion of a significant change should be made from the perspective of a reasonable person with objective knowledge of credible facts, sufficient experience or training and an understanding that the benefits of a marketed product must outweigh its risks.

A significant change could indicate a need for urgent action to, for example:

- modify labelling to include warnings or contraindications
- change packaging to modify the dosing device
- communicate risks to public or health professionals

Consult: Guidance to market authorization holders on issuing health product risk communications

Changes to reference safety information resulting from your signal management processes could also lead to the conclusion of a significant change.

Visit Definitions for an explanation of "significant change".

Acceptable document format for NHP summary reports

You may prepare an ASR using one of the following standardized document formats:

- Periodic benefit-risk evaluation report (PBRER) format
    - preferred international format for drug summary safety reporting
    - follow the standards defined in the ICH E2C (R2) guidance (PDF)
- Periodic safety update report (PSUR) format
    - EU format acceptable and comparable to the PBRER format

You may also prepare an ASR using a non-standardized format, as long as it respects the expected content outlined in this guidance.

Although the PBRER document format is preferred, the format you choose will depend on the nature of the product and your preference.

You may use two consecutive 6-month summary reports prepared for another regulatory authority to meet the regulatory requirements.

Although standardized periodic summary reports such as PBRERs and PSURs are used globally, regional differences may exist. You should consider the need for a Canadian-specific section or addendum when preparing an ASR in these formats. If using a global

PBRER or PSUR prepared for a period greater than one year, the Canadian-specific information must be annualized to meet the regulatory requirements.

Notification of significant change – NHPs

You are encouraged to inform us without delay if there's a significant change in what is known about the risks and benefits of the NHP.

To avoid overburdening the system, do not submit a notification of significant change unless it meets the threshold outlined in the definition of significant change.

Issues related to the quality of the product or good manufacturing practices (GMP) are not in scope of this requirement and should not be notified in this manner.

Visit Definitions for an explanation of "significant change".

If you have questions about what constitutes a significant change, contact us for advice.

How to notify

When informing us of a significant change, the information should be clear and explicit and should contain a description of:

- the significant change
- how the significant change was identified

You are also encouraged to include in your notification the following:

- clinical impacts of the issue on patient or public health, or impact on the product's benefit-risk profile
- any significant impact on product, including in other jurisdictions, for example:
    - recommended use
    - formulation
    - risk information
- what further assessments may be needed in the Canadian context

- follow-up actions needed in Canada with proposed timelines, if applicable, including:
    - changes to packaging, labelling, terms of market authorization, product design or product accessibility
    - risk communication

Note: You are expected to proceed with any intended actions outlined in your notification in accordance with procedures outlined in the NHPR.

To notify us of a significant change, complete the form:

- Notifying Health Canada of a significant change in what is known about the risks and benefits of a product

The **form** is available upon request by emailing no-reply.MHPD.publications.DPSC.non-reponse@hc-sc.gc.ca. To receive the form automatically, the subject line must be exactly "Notifying Health Canada of a significant change form". Do not modify the subject line, as this may prevent the form from being delivered automatically.

Once complete, submit the form without delay as per the instructions included.

Contact us if you have questions about your submission or how to submit.

Discontinued NHPs

After an NHP licence is discontinued or cancelled, you should continue to prepare an ASR until the expiry date of the last lot sold. You are also encouraged to inform us immediately if there's a significant change.

Some adverse reactions and associated safety signals may appear soon after use of the product starts, while others may take longer to appear. For example:

- Late reactions that occur rarely or not at all at the beginning of use, but whose incidence increases with continued or repeated exposure.
- Delayed reactions become apparent some time after a product is used, even if it's withdrawn before the reaction appears.
- Interactions may occur with health products that have not previously been taken or combined.

Submitting annual summary reports

When to submit an annual summary report

Market authorization holders (MAHs) and licence holders must maintain all annual summary reports (ASRs) on site or ensure they're easily accessible.

Although ASRs must be prepared annually, they are **only** to be submitted:

- upon our request
- to fulfill a term or condition imposed by the Minister under the Food and Drug Regulations

Note: ASRs submitted as data to support a market entry submission or application, or to support a supplement to a submission (for example a change to labelling, packaging or indication) are out of scope of this guidance document. For more information on supporting data for a submission or application, consult:

- Guidance on management of drug submissions and applications
- Guidance Document: Post-Notice of Compliance (NOC) Changes: Safety and Efficacy Document (for pharmaceutical, biologic and radiopharmaceutical drugs for human use only)
- Natural Health Products Management of Applications Policy
- Natural Health Product Licence Amendment and Notification Form User Guide

Submitting annual summary reports under the Food and Drug Regulations

To assess the safety or effectiveness of a drug, we may ask you to provide an ASR or case reports relating to adverse drug reactions and serious adverse drug reactions known to you. This is set out in sections C.01.018(5) and (6) of the Food and Drug Regulations (FDR).

The ASR must be submitted within the period specified in our request letter. You will have an opportunity to provide comments on the period outlined in the request letter for the submission of the report.

The request letter may also specify supporting documents to accompany the submission of the ASR.

The review of an annual summary report may help us track post-market follow-up actions, resolve questions about safety issues and monitor safety issues closely.

Submitting annual summary reports under the Natural Health Products Regulations

If we have reasonable grounds to believe that the NHP may no longer be safe when used under the recommended conditions of use, we may ask you to provide a copy of any ASR prepared. This is set out in sections 24(3) of the Natural Health Products Regulations (NHPR). The ASR must be submitted to Health Canada within 30 days of the request.

ASR note to reviewer

An ASR note to reviewer should accompany the submission of all ASRs.

The ASR note to reviewer should include:

- unique product identifier (such as DIN, NPN or DIN-HM)
- the reason for submission
- submission details such as the final sign-off date, data lock point and period covered by the ASR
- additional information including the status of review of the submitted documents in other jurisdictions (where relevant) and any other details that would aid the review

The **ASR note to reviewer template** is available upon request by emailing no-reply.MHPD.publications.DPSC.non-reponse@hc-sc.gc.ca. Ensure that only the exact text "ASR note to reviewer template" is in the subject line of the email.

How to submit annual summary reports

ASRs should be provided to Health Canada in either English or French.

For DIN products, submit the ASR with the ASR note to reviewer in an electronic common technical document (eCTD) or non-eCTD format via the electronic submissions gateway (ESG) using the regulatory enrolment process (REP).

For information on transactions in eCTD or non-eCTD format, consult:

- Filing submissions electronically

For NPN or DIN-HM products, our request letter will outline instructions on how to submit the ASR with the ASR note to reviewer.

Contact us if you have questions about your submission.

Note: There may be instances when the MAH or licence holder contracts another party to carry out certain activities on their behalf. Activities could be maintaining records on adverse reaction data, conducting pharmacovigilance activities or preparing or submitting ASRs. Even if this is the case, the MAH or licence holder must ensure that documents requested by Health Canada are sent within the timeframe requested.

Foreign reviews

When submitting ASRs, you should provide, if available, reviews by the United States (Food and Drug Administration) or European Union (European Medicines Agency) of:

- periodic summary reports or equivalent
- safety assessments

If FDA or EMA reports are not available you should send an available review from another foreign regulatory authority, if available, in English or French.

You should provide these foreign reviews at the same time you submit the ASR. Inform us if a foreign review report becomes available soon after the submission.

Issue-related and interim summary reports

Issue-related summary reports (FDR)

The issue-related summary report (IRSR) is a concise, critical analysis of the adverse drug reactions and serious adverse drug reactions to a drug that are known to the manufacturer and that concern a specific issue identified by the Minister.

Health Canada may ask the manufacturer of a drug to submit an IRSR if we wish to assess the drug's safety and effectiveness. This is set out in C.01.019(1) of the Food and Drug Regulations (FDR).

Content of an IRSR

An IRSR should consider the following:

- actions already taken in relation to the issue
- medical definition of the adverse reactions related to the subject of the report
- description of the search strategy to retrieve the cases (for example, from databases)
- detailed summary analysis of the cases, which should include the following information:
    - tabulation of all events
    - your comments on the cases
    - summary analysis of the temporal relationship between product administration and the occurrence of the event
    - summary analysis of possible risk factors and confounding variables
- summary of medication errors, including incidents without clinical consequences
- Canadian and international patient exposure data using both patient-years and total number of patients exposed, if available
- core reference safety information, approved product labels or other documentation that reflects Canadian market entry requirements

- reference safety information includes company core safety information, company core data sheet
- other documentation includes product monograph, labelling standard or approved labelling information

- conclusion on the product's safety and effectiveness related to the occurrence of these events and, if applicable, any planned risk mitigating actions or change to the risk management plan (RMP), product monograph, labelling, packaging or product design

You may include additional information in the IRSR relevant to the analysis of the specific issue.

If we require other specific information, we will stipulate this in the request letter.

Submission of issue-related summary reports

We will issue a request for an IRSR in writing. You will have an opportunity to provide comments on the period or the requested data outlined in the request letter for the submission of the report.

In general, IRSRs are to be submitted within a 30-day period. However, we may require the information within less than 30 days if it is needed to determine whether the drug poses a serious and imminent risk to human health.

Provide the IRSR in either English or French.

Submit the IRSR in an electronic common technical document (eCTD) or non-eCTD format via the electronic submissions gateway (ESG) using the regulatory enrolment process (REP).

For information on transactions in eCTD or non-eCTD format, consult:

- Filing submissions electronically

Contact us if you have questions about your submission.

Interim summary reports (NHPR)

We may request an interim summary report if we believe the natural health product (NHP) is no longer safe when used under the recommended conditions of use. This is set out in subsection 24(3) of the NHPR. We will inform you of the request in writing.

Since the date of the most recent summary report, the interim summary report must contain a concise critical analysis of all:

- adverse reactions that occurred in Canada
- serious adverse reactions that occurred in Canada and serious unexpected adverse reactions that occurred inside or outside of Canada
    - during the previous 12 months **and**
    - at a dose used or tested for the diagnosis, treatment or prevention of a disease or for modifying organic functions in humans

Submission of interim summary reports

Interim summary reports are to be submitted within a 30-day period.

Interim summary reports should be provided to Health Canada in either English or French.

For NPN or DIN-HM products, our request letter will outline instructions on how to submit the ISR.

Contact us if you have questions about your submission.

Definitions and resources

Definitions

Adverse reaction:

A noxious and unintended response to a marketed health product covered by this document. Includes "adverse drug reaction" as defined in the Food and Drug Regulations (FDR) and "adverse reaction" as defined in the Natural Health Products Regulations (NHPR).

Discontinue:

In respect of the sale of a drug by the manufacturer to whom a document was issued under subsection C.01.014.2(1) that sets out the drug identification number assigned for the drug, to permanently cease the sale of the drug.

Drug:

According to the Food and Drugs Act (act), a drug includes any substance or mixture of substances manufactured, sold or represented for use in:

- diagnosing, treating, mitigating or preventing a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals
- restoring, correcting or modifying organic functions in human beings or animals or
- disinfecting premises in which food is manufactured, prepared or kept

European Union reference date (EURD):

For a medicine containing that active substance or that combination of active substances, corresponds to the:

- date of the first marketing authorization of a medicine containing that active substance or that combination of active substances in the EU **or**
- earliest of the known dates of the marketing authorizations

International birth date (IBD):

Date of the first marketing authorization for any product containing the active substance granted to any company in any country in the world.

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. This is carried out by developing and implementing harmonized technical guidelines and standards for developing, registering and monitoring pharmaceutical products. Health Canada is committed to adopting and implementing ICH guidance.

Licence holder:

The entity that holds the natural product number (NPN) or homeopathic medicine number (DIN-HM).

Market authorization holder (MAH):

The entity that holds the notice of compliance or drug identification number (DIN).

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 errors 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.

Natural health product (NHP):

A substance set out in Schedule 1 of the NHPR or a combination of substances in which all the medicinal ingredients are substances set out in Schedule 1, a homeopathic medicine or a traditional medicine that is manufactured, sold or represented for use in:

- diagnosing, treating, mitigating or preventing a disease, disorder or abnormal physical state or its symptoms in humans
- restoring or correcting organic functions in humans **or**

- modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health

An NHP does not include:

- a substance set out in Schedule 2 of the NHPR
- any combination of substances that includes a substance set out in Schedule 2 **or**
- a homeopathic medicine or a traditional medicine that is or includes a substance set out in Schedule 2

Pharmacovigilance:

As defined by the World Health Organization (WHO), the science and activities relating to detecting, assessing, understanding and preventing adverse effects or any other drug-related problems.

Sell:

According to the Food and Drugs Act (act), sell includes:

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

Serious adverse reaction:

A noxious and unintended response to a product covered by this document 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 a medically important event or reaction
- is life-threatening or results in death

Includes "serious adverse drug reaction" as defined in the FDR and "serious adverse reaction" as defined in the NHPR.

Significant change:

Based on new evidence about the benefits or risks of a product, a conclusion by the market authorization holder (MAH) that there is an emerging safety issue requiring urgent action to:

- manage the potential impact of the issue on patient or public health **or**
- maintain the Minister's confidence that the product's benefits outweigh its risks in accordance with the product's authorization

Vulnerable sub-population:

A group of individuals within the general population who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of experiencing adverse health effects from exposure to the drug or natural health product.

Resources

As a starting point, market authorization holders (MAHs) should refer to the most up-to-date versions of the following guidance documents.

Health Canada guidance documents and notices

- Guidance on management of drug submissions and applications
- Filing submissions electronically
- Notice: Adoption of the International Council for Harmonisation (ICH) guidance on periodic benefit risk evaluation report - ICH Topic E2C(R2), as of March 1, 2013
- Reporting adverse reactions to marketed health products
- Good pharmacovigilance practices (GVP) guidelines (GUI-0102)
- Risk classification of good pharmacovigilance practices (GVP) observations (GUI-0063)

International Council for Harmonization (ICH) guidance documents

- ICH E2C(R2): Periodic benefit-risk evaluation report (PBRER)

Contact us

Marketed Health Products Directorate:

Regulatory Project Management Office (RPMO)

Email: bbrs.rpm-gpr.bbra@hc-sc.gc.ca

- For submissions related to Biologics (including vaccines, fractionated blood products, biotherapeutics, biosimilars), Radiopharmaceuticals, Pharmaceuticals (non-prescription) and Natural Health Products

Email: mpb.rpm-gpr.bppc@hc-sc.gc.ca

- For submissions related to Pharmaceutical (prescription) products, including generics and controlled substances

Office of Submissions and Intellectual Property (OSIP)

Email: ereview@hc-sc.gc.ca

- For information on submission processing

Business Facilitation and Modernization Directorate (BFMD):

Business Informatics Division (BID)

Email: ereview@hc-sc.gc.ca

- For information on filing submissions electronically

General inquiries

For inquiries about this guidance document, include the phrase "Guidance on preparing and submitting summary reports for marketed drugs and natural health products" in the subject line. Submit your request by email: mhpdpolicy-politiquesdpsc@hc-sc.gc.ca.