Health Canada Santé Canada

Format and content for post-market drug benefit-risk assessment in Canada

Guidance document

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.

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Publication date: February 2019

Cat.: H164-255/2019E-PDF
ISBN: 978-0-660-28704-1
Pub.: 180752

Forward

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada's mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document **may be** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant programme area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

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1 Introduction

1.1 Objective

The objective of this guidance document is to assist Market Authorization Holders (MAHs) in developing a post-market benefit-risk assessment for a marketed drug when requested.

Note: The information provided in this document is different from the guidance documents related to a Periodic Safety Update Report (PSUR) or a Periodic Benefit-Risk Evaluation Report (PBRER) although there are sections that may be utilized or re-used from the PSUR or PBRER (see Appendix 1).

1.2 Scope

This guidance document is intended for the following therapeutic product lines: prescription and non-prescription pharmaceutical drugs, biologic drugs, radiopharmaceuticals and vaccines. Medical devices and natural health products are excluded from this Guidance Document because their regulatory requirements are different from those of pharmaceutical drugs.

1.3 Background

To improve consistency and transparency, and to facilitate the decision-making process, Health Canada has produced this Guidance on Format and Content for Post-Market Drug Benefit-Risk Assessment in Canada, as a more detailed and structured approach to the presentation of benefit-risk assessments. It provides an outline of how to respond to a Health Canada request for a benefit-risk assessment, for example, made pursuant to section C.01.013 of the Food and Drug Regulations or section 21.31 of the Food and Drugs Act and section C.01.052 of the Food and Drug Regulations.

1.3.1 Benefit-Risk Assessment as Part of the Health Product Lifecycle

Benefit-risk assessments, as described in this guidance document, are usually triggered by multiple factors and may lead to a significant change in market status of the product (product withdrawal by the MAH or cancellation of the Drug Identification Number by the Director under C.01.014.6 (2)(b)) or risk mitigation approaches such as label changes and/or risk communications to the public and healthcare professionals. The new information obtained through a benefit-risk assessment will contribute toward maximizing the product's safety and effectiveness throughout its lifecycle.

1.3.2 Purpose of a Benefit-Risk Assessment

The purpose of a benefit-risk assessment is to determine whether sufficient evidence exists to demonstrate that the benefits of a product continue to outweigh the risks. Sufficiency of evidence for a product to maintain a positive benefit-risk profile will be outlined by Health Canada as a part of the benefit-risk assessment process/request.

1.3.3 Regulatory Background

A benefit-risk assessment may be requested voluntarily or under the authority of the Food and Drugs Act; for example, under the following sections:

Food and Drugs Act:
(https://laws-lois.justice.gc.ca/eng/acts/F-27/)

Section: **21.31**

Food and Drug Regulations:
(https://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/index.html)

Section: **C.01.052** :
An explanation of the issuance of Ministerial Orders can be found in Amendments to the Food and Drugs Act: Guide to New Authorities (https://www.canada.ca/en/health-canada/services/drugs-health-products/legislation-

guidelines/amendments-food-drugs-act-guide-new-authorities-power-require-disclose-information-power-order-label-change-power-order-recall.html). The procedure normally involves a discussion with the manufacturer, including an opportunity to comply voluntarily, before an order is issued.

And section **C.01.013:**
A request by the Minister under C.01.013 is normally made after only discussion with the manufacturer of the issue relating to the drug.

2 Preparing a Post-Market Benefit-Risk Assessment

This guidance outlines how to organize the information that is generally requested by Health Canada as part of a benefit-risk assessment. Depending on the situation, Health Canada may make additional requests. The manufacturer to whom the request is addressed is only responsible for providing evidence to support a benefit-risk assessment of their own product. If Health Canada is assessing the benefit-risk of a broader group of products, for example, with the same active ingredient(s), each manufacturer will be subject to the same requirements for their own product(s). The information below outlines the recommended information for each section of the assessment.

2.1 Background Information

This section describes background information for the product, including its use, previous safety interventions, if any, and the disease(s)/condition(s) for which the product is used. It describes or cites other possible therapeutic health product options compared or discussed in the benefit-risk assessment and their place in patient therapy.

2.1.1 Purpose

This section provides a brief overview of the main issue(s) that led to the request of the benefit-risk assessment.

2.1.2 Product Information

This section describes the product being evaluated. This information could include indications authorized in Canada, product class information, formulation and/or labelling information relevant to the safety risk under review (Contraindications, Adverse Events, etc.). Other indications authorized by other jurisdictions should also be included.

2.1.3 Regulatory History

This section describes the regulatory history of the product, including the current regulatory and marketing status of the product in Canada, as well as in other jurisdictions and date(s) of market authorization (internationally and in Canada).

2.1.3.1 Current Risk Mitigation Strategies

This section provides information on the previous and current mitigation strategies that were in place leading up to the benefit-risk assessment. These can include, but are not limited to, the labelling in the most recent Canadian Product Monograph, any available educational materials and any risk communications that may have been issued.

If applicable, key differences between Canadian and other International Council for Harmonization (ICH) members' labelling should be highlighted. Relevant issues should be listed that have been addressed through past regulatory interventions in Canada as well as in other jurisdictions.

2.1.4 Exposure Estimates

This section includes exposure information:

- For international jurisdictions, as well as Canadian specific data if it is available,
- An explanation of how exposure was calculated should include the following information:
    - The data that were used;
    - How the data were used;
    - The start and the end dates that were used for the calculation.
- A comparison between Canadian and international exposure rates noting any relevant confounders and/or biases that could have affected the rates.

2.1.5 Information on the Disease(s) or Condition(s)

This section describes the underlying disease(s)/condition(s) for which the product is used. This should include Canadian specific information, if available. This section could comprise, for example:

- Symptoms and signs;
- Population in which the indication applies;
- Pathophysiology;
- Epidemiology (including risk factors as well as Canadian and international incidence and prevalence rates).

This section should also include a brief description of how the disease/condition is managed including treatment options for individual patients/populations, as well as the uncertainties of the disease and its therapies.

2.1.6 Other Therapeutic Options

This section provides background information on other relevant medical therapies, including their benefits and risks as listed on their product labels. This information is for comparison within the benefit-risk assessment. Other topics that can be included, if available, are barriers to safe and effective use or patient preference. This information should be included for relevant medical therapies that are authorized for use in Canada. Any off-label treatments that are used to treat the condition should be discussed as well, to provide additional context. The manufacturer may refer to relevant treatment guidelines issued by Canadian medical associations when available.

2.2 Evaluation of Benefit

2.2.1 Characterization of Benefit(s)

This section identifies:

- The intended benefits of the product for the authorized indication;
    - For example, to prevent disease, to treat an acute condition to reduce risk of a serious outcome, to reduce or stabilise a chronic disorder.
- Any potential effects on related, subsequent or more serious conditions;
- Information regarding health product efficacy/effectiveness from either pre- or post-market evidence;
    - This should include information regarding the strength of the evidence of efficacy, for example: data derived from clinical studies, systematic reviews and meta-analyses (of clinical trials or observational studies) and/or therapeutic effectiveness studies. References such as Cochrane may be used in discussing quality or strength of evidence.
- Information regarding health product real-world effectiveness from post-market evidence.

Include the following in this section, which is listed in no particular order:

- Population in which the indication applies;
- Known/relevant pharmacological properties of the product and metabolites;
- Identification of trends, patterns and/or correlations of the benefits being assessed;
- Consistency of the data;
- Identification of bias and confounding factors;
- Comparisons between efficacy and effectiveness;
- Role of the product in providing a benefit in the context of Canadian medical practice;
- Primary and secondary efficacy, therapeutic outcomes (endpoints);
- Anticipated or potential benefits;
- Improvement in patient-reported outcomes;
- Improvement in adherence, persistence, and/or ease of use.

2.2.2 Discussion of Comparative Benefits

If the information is available, this section may be useful in providing contextual information relating to a benefit-risk assessment as it compares the efficacy/effectiveness of the product (or class if applicable) with:

- No intervention;
- Other conventional therapies or interventions.

A description of the evidence, either pre- or post-market, of comparative efficacy/effectiveness benefits for the authorized indication(s) should be included. In addition to the Phase I-III clinical trials, the description could include:

- Phase IV clinical trials (where applicable);
- Systematic reviews and meta-analyses of observational studies;
- Comparative therapeutic effectiveness observational studies;
- Data selection process;
- Quality of evidence.

Studies related to the products that are not included in the analysis need to be explicitly identified and the justification for their exclusion must be clearly presented.

If available, provide information on comparative effectiveness, which should include evidence of product uniqueness or evidence of a limited population where there is a recognised benefit over comparator products or other available treatments, e.g.:

- Study design and methodologies;
- Statistical and clinical significance of results;
- Adequacy of statistical methodology and analysis;
- Consistencies and inconsistencies between effectiveness and efficacy data in pre-market submissions;
- Relationship between short- and long-term benefits;
- Efficacy versus effectiveness;
- Exposure response relationships;
- Methodologies for synthesising research evidence;
- Compliance with best practices (e.g. Cochrane) for conducting systematic reviews of observational studies;
- Adequacy of methodologies for combining data from different observational designs;
- Methodologies for combining observational data with randomised clinical trial data.

Other factors that should be considered in analysing the comparative benefits are:

- Adverse drug reactions / confirmed signals;
- Important identified risks;
- Important potential risks / pharmacological class effects;
- Decline in patient-reported positive outcomes;
- Decrease in adherence, persistence, and/or ease of use;
- Lack of efficacy.

2.3 Evaluation of Risk

2.3.1 Characterization of the Identified Risk

This section identifies the issues to be discussed, focussing on the issue that prompted the benefit-risk assessment. For the issue (identified risk), provide a brief medical summary, including as appropriate information on the epidemiology, clinical characteristics, medical seriousness, associated outcome (reversibility, morbidity, mortality), duration, preventability, predictability, measurability, capacity to monitor the issue, uncertainties in the benefit-risk assessment and known risk factors if not presented previously. Any unknowns/missing information should also be identified.

The evidence regarding the issue (identified risk) should be described and critically analysed, starting with the most pertinent evidence. The type of evidence may depend on the nature, incidence, and/or severity of the adverse event. When multiple types of evidence are available, it is recommended to present the higher quality evidence first, and then proceed to lesser grades of evidence. Discuss the validity of the evidence, which can include:

a) Meta-analyses and systematic reviews:
   - Source and type of data. Briefly describe search strategies/terms used for literature;
   - Study design and methodologies, including source of data, selection criteria, weighting, risk differences or rate differences (if available) etc.;
   - Statistical and clinical significance of the results (if feasible and meaningful);
   - Limitations in study design, implementation or interpretation.

b) Clinical trial data, especially Phase IV studies:
   - Source and type of data. Briefly describe search strategies/terms used for literature;
   - Study design and methodologies, including study quality, with information such as endpoints used, length of treatment and follow-up, and dropout rates;
   - Incidence/prevalence of the safety issue in clinical trials versus placebo or other treatments;
   - Statistical and clinical significance of the results;
   - Consistency between studies;
   - Study selection process;
   - Limitations of the clinical trial data (e.g. sample sizes, populations excluded, duration of follow-up, etc.).

c) Observational studies:
   - Source and type of data. Briefly describe search strategies/terms used for literature;
   - Study design and methodologies, including study quality, with information such as endpoints used, length of treatment and follow-up;
   - Incidence/prevalence of the safety issue;
   - Clinical/scientific significance of risk quantification;
   - The clinical/scientific validity of the study(ies), including methods of adjusting for potential biases and confounding factors, such as missing data.

d) Adverse Drug Reaction Reports:
   - Source and type of data: spontaneous post-market adverse drug reaction (ADR) reports, grouped according to the System Organ Class (SOC) or Medical Dictionary for Regulatory Activities (MedDRA) classification scheme where appropriate;
   - Reporting period, search strategies, and/or Standardized MedDRA Query (SMQ) terms;
   - Number, nature and outcome of (relevant) serious cases;
   - Trends, patterns and/or correlations of ADRs within relevant subgroups (e.g. age, sex, dose, predisposing risk factors, latency, duration of therapy, demographics, concomitant therapeutic products, pre-existing medical conditions, overdose and/or food or therapeutic product interactions and incidence/prevalence in the unexposed population);
   - Summary of key case reports;
   - Causality assessment of selected cases;
   - Quantitative analyses of the association, where feasible (e.g., the reporting rate, proportional reporting ratio, reporting odds ratio, information component (IC) & IC025, etc.);
   - Limitations of ADR reports and quantitative analyses (e.g. quality of reports, reporting rates, missing information, data-mining assumptions, validity.).

2.3.2 Considerations of the Issue (Identified Risk)

This section summarizes the evidence regarding the safety issue. Discussions could include:

- Relevant pharmacological properties of the product as well as its metabolites, (e.g. known/proposed mechanism(s) of action, possible class effect);
- Product overdose;
- Susceptible/vulnerable populations including pharmacogenomics;

- Pertinent exposure/utilization data;
- Authorized versus off-label use;
- Practice or treatment issues associated with the product;
- Quantitative strength of the association between the product use and the identified safety issue;
- Assess the strength and the quality of the evidence. References such as e.g., Cochrane or GRADE, may be used as applicable.

2.3.3 Discussion of Comparative Risks

This section may be useful in providing contextual information relating to a benefit-risk assessment as it compares the issue(s) (identified risk) of the product (or class if applicable) to risk issues (if information is available) associated with:

- Other conventional therapies;
- Surgical treatments/other interventions;
- No intervention;
- Other considerations.

2.4 Evaluation of the Benefit-Risk Profile

2.4.1 Summary and Analysis of the Benefit-Risk Profile for the Identified Risk

This section provides context and justification for the overall decision on the benefit-risk profile of the product. It should include a summary of the key benefits and the key risks of the product listed in order of priority, and, where relevant, supporting explanation. This section should also compare the benefits and risks for the product when it is used under authorized indications for each issue, from such sources as:

- Meta-analyses and systematic reviews;
- Clinical trial data, including Phase IV studies;
- Observational studies;
- Adverse Drug Reaction reports (international sources first, followed by Canadian sources).

The quality of the evidence should be captured in this section (e.g. if a well-designed Phase IV study is being compared to a poorly designed meta-analysis). The discussion should include the distinction between data and value judgements used to interpret the degree of benefit versus the degree of harm, as well as the impact of uncertainty on the assessment. References may be used, as applicable, e.g. Cochrane.

2.4.2 Quantitative Benefit-Risk Analysis

Specific quantitative or semi-quantitative methodologies are not required for benefit-risk assessments at this time; however, they may be included in submissions to support the benefit-risk assessment. A detailed description of the methodologies, software, references and analysed data should be appended. Discuss results from any quantitative or semi-quantitative methodologies used to perform a benefit-risk assessment on the product. Include a brief rationale for why each methodology was used.

2.4.3 Benefit-Risk Analysis in Context

This section should describe the evolution of the known benefits and risks of the product at the time of authorization, compared with present knowledge, e.g., new risk data or comparison with newer drugs. Similar parameters and outcome measures should be used whenever possible. Factors to consider may include:

- Benefits and risks in the context of current medical practice;
- Change in what is known about the product's benefits and risks;
- Limitations of the benefit-risk assessment (e.g. important uncertainties or unknowns).

2.5 Conclusions and Risk Mitigation Options

2.5.1 Conclusions

Summarize the conclusion developed through the benefit-risk analysis of the product with a brief rationale, stating whether the overall benefit-risk profile for the product has changed and, if so, how.

2.5.2 Risk Mitigation Options

If applicable, describe possible risk mitigation options if the overall benefit-risk profile has changed.

3 For Further Information

If you have questions or comments about this document, they may be directed to:

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Appendix 1: Sections that may be utilized or re-used from the Periodic Safety Update Report (PSUR) or Periodic Benefit – Risk Evaluation Report (PBRER)

Benefit-Risk Assessment	Periodic Safety Update Report (PSUR)	Periodic Benefit-Risk Evaluation Report (PBRER)[1]
Background information: product information, its use, exposure estimates, previous safety interventions, the disease(s)/condition(s), and other therapeutic options	Sections: 1, 3, 4, 5	Sections: 1, 3, 4, 5
*Characterization of the safety issue: analysis and evidence of the safety issue including medical background	Not Included	Not Included
Evaluation and Characterization of Benefit(s): evidence of efficacy and effectiveness, relevant pharmacological properties of the product and metabolites, comparison with alternative therapies supported by data from clinical trials and observational studies	Not Included	Section 17 (requiring enhanced analysis)
*Evaluation of and Characterization of Risk(s): associated risks that have been identified in both pre- and post- market settings	Not Included	Sections: 13, 15, 16
Evaluation of Benefit-Risk Profile: provides context and justification for the overall decision on the benefit-risk profile of the product, quantitative or semi-quantitative analysis required	Not Included	Section 18 (requiring enhanced analysis)
Final Conclusions and Risk Mitigation Options: follow up measures including an impact analysis	Not Included	Section 19 (requiring enhanced analysis)

*Information may be present in the Risk Management Plan (RMP) for the product.

Appendix 2: Definitions and Abbreviations

Adverse Event[2]**:** Any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom or disease temporally associated with the use of a drug, whether or not considered related to the medicinal product.

Adverse Drug Reaction[2]**:** For the purpose of this guidance document, an adverse drug reaction refers to a noxious and unintended response to a drug which occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of an organic function.

Benefit[3]**:** Effects that promote physical, emotional or economic well-being.

Benefit-Risk Assessment or Evaluation: A method of evaluating the usefulness of a drug for a specific indication, taking into account the benefits and risks associated with that drug under normal conditions of use.

Causality: A medical assessment of the relationship between an adverse event and a therapeutic product.

Efficacy[4]**:** The ability of a medicine or medical technology to bring about the intended beneficial effect on individuals in a defined population with a given medical problem, under ideal conditions of use.

Effectiveness[4]**:** The effect a medicine or medical technology is purported, or is represented, to have under conditions for the use prescribed, recommended or labelled. Note: Effectiveness refers to how well a drug achieves its intended effect in the usual clinical setting (‘‘real world’’) and reflects its impact in the community (benefits observed at the population level).

Therapeutic Product: For the use of this guidance document, the term “therapeutic product” refers to any medicine, medical technology, medicinal product, prophylactic product or treatment.

Indication for Use: A statement that describes the limitations for use of a therapeutic product, including the disease state, condition(s) or symptom(s) and the target population, if specified, for which the therapeutic product is intended and authorized by Health Canada to be used. The indication for use is part of the Terms of Market Authorization, as identified in the Product Monograph accompanying the Notice of Compliance (NOC) or in the document that assigns a Drug Identification Number (DIN), and any related labelling material.

Market Authorization Holder (MAH)[5]**:** The MAH may also be referred to as the Manufacturer. The MAH is the legal entity that holds the Notice of Compliance, the DIN or that has received authorization to initiate clinical trials in Canada.

Risk[3]: A measure of both the potential harm to human health that may result from being exposed to a product under specific conditions of use, together with the likelihood that harm will occur.

Abbreviations

ADR:	Adverse Drug Reaction
IC:	Information Component
MAH:	Market Authorization Holder
MedDRA:	Medical Dictionary for Regulatory Activities
SMQ:	Standardized MedDRA Queries
SOC:	System Organ Class

Appendix 3: References

1 **The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)**. ICH guideline E2C (R2) Periodic benefit-risk evaluation report (PBRER). Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2012**.**

2 **Health Canada**. Reporting Adverse Reactions to Marketed Health Products - Guidance Document for Industry. [Online] May 23, 2018. [Cited: October 19, 2018] https://www.canada.ca/en/health-canada/services/drugs-health-products/reports-publications/medeffect-canada/reporting-adverse-reactions-marketed-health-products-guidance-industry.html

3 **Health Canada**. Health Canada Decision-Making Framework for Identifying, Assessing and Managing Health Risks. [Online] February 25, 2011. [Cited: October 19, 2018]. https://www.canada.ca/en/health-canada/corporate/about-health-canada/reports-publications/health-products-food-branch/health-canada-decision-making-framework-identifying-assessing-managing-health-risks.html

4 **CIOMS IV**. Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals. Switzerland : Council 548 for International Organizations of Medical Sciences, 1998. https://cioms.ch/wp-content/uploads/2017/01/benefit-risk.pdf

5 **Health Canada**. Guidance for Industry: Issuance of Health Professional Communications and Public Communications by Market Authorization Holders. [Online] May 28, 2010. [Cited: October 19, 2018]. https://www.canada.ca/en/health-canada/services/drugs-health-products/reports-publications/medeffect-canada/guidance-document-industry-issuance-health-professional-communications-public-communications-market-authorization-holders-health-canada-2010.html