Guidance Document for Developing a Post Market Benefit-Risk Assessment

Draft Version Date: 2014-02-14
1 Introduction

1.1 Objective

The objective of this guidance document is to assist Market Authorization Holders (MAHs) in developing a benefit-risk assessment for a marketed health product when submitting a requested or voluntary benefit-risk assessment.

1.2 Scope

This guidance document is intended for, but not limited to, the following product lines: pharmaceuticals, biologics, biotechnology products and vaccines.

This guidance document is intended to refer to a benefit-risk assessment that has been requested through the Food and Drug Regulations, however, it should be noted that not all requests for a benefit-risk assessment will explicitly refer to the applicable legislation. When the applicable legislation has not been invoked, the guiding principles for the preparation of benefit-risk assessments in this guidance document can still be referenced by the benefit-risk assessment author.

1.3 Background

1.3.1 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 health product outweigh the risks for a given indication. ‘Sufficient’ in this guidance document is derived from use in the Food and Drugs Regulations, applied in recognition that a request for a benefit-risk assessment is not always in the context of a submission for market authorization and can occur throughout the product lifecycle. The term ‘sufficient’ can also vary from issue to issue and can involve both objective and subjective evaluation of the submitted information in the context of available scientific knowledge and medical standards of care.

Health Canada is the federal department responsible for helping the people of Canada maintain and improve their health. One way it achieves this is through its national authority over the market authorization and vigilance of health products. Prior to marketing a health product in Canada, the manufacturer must provide sufficient evidence supporting the safety, efficacy and quality of a health product to meet the requirements of the Food and Drugs Act and its regulations. When a potential or actual shift in the benefit-risk profile is suspected or identified, Health Canada can request a benefit-risk assessment.
A shift in the benefit-risk profile is generally “related to the seriousness, severity or frequency” of a safety issue or a lack of efficacy/effectiveness and can “be expected to result in significant changes in product information or marketing status (e.g. new contraindications, substantial restrictions on indications or treated populations, mandates for further research, or withdrawal of the product from use)”\(^1\). Post-market benefit-risk assessments can be requested when a significant or suspected safety concern arises about a marketed health product. Where a benefit-risk assessment is requested from Health Canada, this guidance document will be the recommended method for preparing the benefit-risk assessment unless indicated otherwise.

Note: The information provided in this document is not to be confused with guidance documents related to a Periodic Safety Update Report or a Periodic Benefit-Risk Re-Evaluation Report.

1.3.2 The Need for a Guidance Document on Post-Market Benefit-Risk Assessments

In the past, benefit-risk assessments have been requested using the Council for International Organizations of Medical Sciences Working Group IV (CIOMS IV) for guidance\(^1\). The resulting benefit-risk assessments have varied in format and content. To improve transparency and to facilitate the decision-making process, Health Canada has produced this Guidance Document for Post-Market Benefit-Risk Assessments as a more detailed and structured approach to the presentation of benefit-risk assessments.

1.3.3 Regulations

The section of the Food and Drugs Regulations that refers to the request of a legislatively mandated post-market benefit-risk assessment, either directly or indirectly is found in C.01.013. It should be noted that not all requests for a benefit-risk assessment will be requested after this legislation has been invoked. Use of C.01.013 generally involves discussion between Health Canada and the MAH prior to its invoking.

**Food and Drug Regulations**

**C.01.013.** (1) Where the manufacturer of a drug is requested in writing by the Director to submit on or before a specified day evidence with respect to a drug, the manufacturer shall make no further sales of that drug after that day unless he has submitted the evidence requested.

(2) Where the Director is of the opinion that the evidence submitted by a manufacturer, pursuant to subsection (1), is not sufficient, he shall notify the manufacturer in writing that the evidence is not sufficient.

(3) Where, pursuant to subsection (2), a manufacturer is notified that the evidence with respect to a drug is not sufficient, he shall make no further sales of that drug unless he...
submits further evidence and is notified in writing by the Director that that further evidence is sufficient.

(4) A reference in this section to evidence with respect to a drug means evidence to establish the safety of the drug under the conditions of use recommended and the effectiveness of the drug for the purposes recommended.

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

The MAH has an obligation to monitor the product for any information about unanticipated adverse effects, and will be subject to ongoing monitoring by Health Canada post-market. Continual surveillance is important because many health products are found to have unanticipated adverse effects after they are marketed. If a shift in the benefit-risk profile is identified, it is possible that Health Canada will request further information to assess the safety, effectiveness and/or quality of the health product. Benefit-risk assessments, as described in this guidance document, are generally triggered by a complex set of factors and generally lead to significant changes in market status. Regardless of the complexity of a benefit-risk assessment, such information will contribute towards maintaining the health product’s safety and effectiveness throughout its lifecycle.
2 Guidance for the Preparation of a Post-Market Benefit-Risk Assessment

This guidance provides a schema to organize the information that Health Canada would generally request as part of a benefit-risk assessment. This list is not comprehensive, however, and a benefit-risk assessment request from Health Canada is not limited to this information.

2.1 Background Information

This section describes background information for the health product, its use, previous safety interventions and the disease(s)/condition(s) for which the health product is used. It also provides background information on other therapeutic options that are compared or discussed in the benefit-risk assessment.

2.1.1 Purpose

Provide a brief overview of the main intent/purpose of the benefit-risk assessment. This can include a brief description of the issue(s) that led to the request or need for a benefit-risk assessment.

2.1.2 Product Information

Describe the health product under investigation. This could include relevant Canadian indications, product class information and/or pertinent labelling information (Contraindications, Adverse Events, etc.).

2.1.3 Regulatory History

Describe the regulatory history of the product, identifying the current regulatory status of the health product in Canada and in other jurisdictions, year of market authorization (internationally and in Canada) and the date of marketing in Canada. This could include highlighting key differences between Canadian and international labelling, listing relevant issues that have been addressed through past regulatory interventions in Canada and in other jurisdictions (such as labelling updates, special access programs and other risk mitigation strategies), etc.

2.1.4 Exposure Estimates

Include exposure information in Canada and other jurisdictions and explain how exposure was calculated. This section could include a comparison between Canadian and international exposure rates as well as relevant confounders and biases that could have affected the rates.
2.1.5 Disease Information

Describe the underlying disease(s)/condition(s) for which the health product is used. This section could include but is not limited to the following:

- Symptomatology (symptoms and signs)
- Pathophysiology
- Epidemiology (Including risk factors as well as Canadian and international incidence/prevalence rates)

Provide a brief description of how the disease/condition is managed by afflicted individuals/populations.

2.1.6 Other Therapeutic Options

Provide background information on relevant medical and surgical therapies for comparison within the benefit-risk assessment.

Provide a brief description of how the disease/condition is managed through other therapeutic options. This can include topics such as factors of convenience or patient preference.

2.2 Evaluation of Benefit

This section describes the benefits, in terms of both efficacy (from pre- or post-market evidence) and effectiveness, which contribute to the overall benefit-risk assessment. This section could provide information on the purpose or intended outcome of the treatment, the evidence of the product’s efficacy and effectiveness for the health product’s authorized indication, the evidence for comparative efficacy and effectiveness, as well as ancillary evidence supporting efficacy and effectiveness in specific populations in the context of Canadian medical practices, etc. Present and discuss each benefit separately if more than one benefit is being discussed.

This section could include (among other topics):

- A statement about the intended purpose and impact of the product on the outcome(s) of the authorised indication. (See the CIOMS IV checklist: Purpose or intended outcome of the treatment for more robust example information to include)
- A description of the potential impact of the therapy directly on related and subsequent more serious conditions, both in terms of intended/unintended benefits.
- When a product has multiple benefits, each type of benefit (i.e. overall survival, quality of life, etc.) should be presented and discussed separately, but multiple endpoints for the same benefit should be presented together.
• A stratification of the evidence by comparator for clinical trial data, meta-analyses and post-market observational studies (placebo versus comparator or other intervention-based treatment).

• Information should be organized systematically, for example, by comparator (placebo, active treatment(s)) and for each comparator by source of data (clinical trials, meta-analyses, post-market observational studies). The organization should be similar manner for each type of benefit.

2.2.1 Characterization of Benefit(s)

Identify the intended purpose and impact of the product on the outcome(s) of the authorised indication (e.g. to prevent disease, treat an acute condition to reduce risk of a serious outcome, to reduce or stabilise a chronic long term disorder, etc.)

Identify the benefit(s) to be discussed with an emphasis on efficacy (either from pre- or post-market evidence) and effectiveness (from post-market evidence). Describe the evidence of efficacy. The evidence can include (but is not limited to) clinical trial data, systematic reviews and meta-analyses (of clinical trials or observational studies) and/or therapeutic effectiveness studies.

Additional points when discussing the benefits of a health product could include (but are not limited to):

• Known/relevant pharmacological properties of the product and metabolites
• Trends, patterns and/or correlations of the benefits under study
• Quantitative strength of the association
• Consistency/granularity of the data
• Identification of bias and confounding factors
• Comparisons between efficacy and effectiveness characterization
• Role of the product in providing a benefit in the context of Canadian medical practice

2.2.2 Comparison of Benefits

Compare the efficacy/effectiveness of the product to (if information is available):

• Other conventional therapies
• Surgical treatments/other interventions
• No intervention
• Other considerations

Describe the evidence of comparative efficacy/effectiveness benefits of results for the authorized indication(s). The evidence could include:

• Phase IV clinical trials (where applicable)
• Systematic reviews and meta-analyses of observational studies
Comparative therapeutic effectiveness observational studies

If possible, provide comparative effectiveness evidence of product uniqueness or a niche population(s) where there is a recognised benefit over comparator products or other available treatments.

Information to consider in describing the above mentioned evidence could include:

- Study design and methodologies
- Statistical and clinical significance of results
- Adequacy of statistical methodology and analysis
- Consistencies and inconsistencies between effectiveness and comparative efficacy data in pre-market submissions
- Relationship between short and long term benefits efficacy vs effectiveness
- Exposure response relationships
- Methodologies for synthesising research evidence
- Compliance with best practices 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

### 2.3 Evaluation of Risk

This section identifies the safety issues to be discussed, focusing on the safety issue(s) that prompted the benefit-risk assessment. Discuss safety issues one at a time, starting with the issue of greatest concern. The evidence that the safety issue represents risk(s) attributable to the product is to be reviewed and discussed in the context of:

- the medical conditions and adverse events associated with the use of the product (including off-label use if relevant)
- specific populations of concern
- the risk(s) associated with alternate treatments

For consistency, the same format for presentation of the evidence is to be used for all identified safety issues. For clinical trial data, post-market observational studies and meta-analyses, stratify the evidence by comparator (placebo versus active treatment(s)) as appropriate.

#### 2.3.1 Characterization of the Safety Issue(s)

Identify the safety issue. Briefly provide background information on the medical nature of the safety issue [adverse event] such as the epidemiology, clinical characteristics, medical seriousness, associated outcome (reversibility, morbidity, mortality), duration,
preventability, predictability, measurability, the capacity to monitor the issue and known
risk factors if not presented previously.

Describe and analyse the evidence regarding the safety issue. Start with the most
pertinent evidence. This will vary depending on the incidence and severity of the adverse
event. For example, with low frequency events such as hepatotoxicity causing liver
failure or death, adverse reaction reports may be the primary source of evidence, whereas
for cardiovascular events that might be more common, clinical trials may be the most
primary source of information. When multiple types of pertinent evidence are available,
it is recommended to present the higher quality evidence at the top of the hierarchy of
evidence first, and then proceed to lesser grades of evidence; however, this is left to the
discretion of the benefit-risk assessment writer. The types of evidence and information to
consider can include:

1. Meta-analyses and systematic reviews:
   - Source and type of data.
   - Study design and methodologies, including source of data, selection criteria,
     weighting, etc.
   - Statistical and clinical significance of the results.
   - Limitations in study design, implementation or interpretation.

2. Clinical trial data, including Phase IV studies:
   - Identify the source of the data (e.g. MAH, literature, etc.). Briefly describe
     search strategies/terms used for literature data.
   - Study design and methodologies.
   - Incidence of the safety issue in clinical trials versus placebo or other
     treatments.
   - Statistical and clinical significance of the results.
   - Consistency between studies.
   - Limitations of the clinical trial data (e.g. sample sizes, populations excluded,
     duration of follow-up, etc.).

3. Observational studies:
   - Nature of the data (abstracts, letters, peer-reviewed articles, etc.).
   - Study design and methodologies (e.g. case control, cohort studies, procedures
     for risk quantification, choice of comparators).
   - Incidence/prevalence of the safety issue and the clinical/scientific significance
     of risk quantification.
   - The clinical/scientific validity of the study(ies), including methods of
     adjusting for potential biases and confounding factors.

4. Adverse Reaction Reports (from international followed by Canadian sources):
• Spontaneously reported post-market adverse reactions (ARs) relevant to the safety issue, grouped according to the System Organ Class (SOC) or MedDRA classification scheme where appropriate. Identify the reporting period. Search strategies, or SMQ defined terms should be identified.
• Number, nature and outcome of (relevant) serious cases.
• Trends, patterns and/or correlations of ARs within relevant subgroups (in consideration of identifiable subgroups, predisposing risk factors, AR predictability, etc.). This can include the following variables: age, sex, dose, latency, duration of therapy, demographics, concomitant health products, pre-existing medical conditions, overdose and/or food or health product interactions.
• Summary of key relevant case reports.
• Causality assessment of selected cases, as warranted.
• Quantitative analyses of the association, where available & feasible (e.g. the Reporting rate Proportional Reporting Ratio, Reporting Odds Ratio, Information Component (IC) & IC025, etc.).
• Limitations of AR reports and quantitative analyses (e.g. quality of reports, reporting rates, missing information, data-mining assumptions, validity, etc.).

2.3.2 Interpretation of the Safety Issue(s)

Summarize and discuss, where relevant, the evidence regarding the safety issue(s). Discussions could include:
• Known/proposed mechanism(s) of action.
• Relevant pharmacological properties of the product/its metabolites.
• Recognized class effect.
• Relevant information related to product overdose.
• Susceptible populations or vulnerable populations including pharmacogenomics.
• Pertinent exposure/utilization data.
• Authorized versus off-label use.
• Practice or treatment issues associated with the product.
• Comparison with alternative treatments.

Repeat the characterization using the same guidelines outlined above for each subsequent safety characterization.

2.4 Evaluation of the Benefit-Risk Profile

This section provides an analysis of the benefit-risk profile based on information discussed in previous sections. This section highlights any information that has not been explicitly identified in previous sections but that could be deemed of use to the benefit-risk analysis being performed.
This section is not intended as a replication of previous sections, it provides context and justification for the overall decision on the benefit-risk profile of the health product.

2.4.1 Summary of the Benefits and Risks

Briefly summarize the key benefits of the health product for this benefit-risk analysis.

Briefly summarize the key risks of the health product for this benefit-risk analysis.

2.4.2 Benefit-Risk Analysis for the Safety Issue(s)

Compare the benefits and risks for the health product when it is used under approved indications. When comparing the benefits and the risks, discuss the benefit-risk balance based on information from the following sources (where applicable):

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

The quality of the evidence should be compared in this section. For example, if a well-designed, Phase IV study is being compared to a poorly designed meta-analysis, discuss this when comparing information for the source. Justify why a study is considered a better study than comparator studies.

2.4.3 Benefit-Risk Analysis in Context

If applicable, compare the benefits and risks of the product at the time of authorization to any modern changes that have influenced the benefit-risk balance (e.g. changes in how a health product is used due to modern surgical techniques).

Compare the benefits and risks of the health product when compared to suitable alternatives (e.g. placebo, other pharmaceutical alternatives, no treatment, etc.). Similar parameters and outcome measures should be used whenever possible.

Contextualize the benefits and risks in terms of modern medicinal practices.

Discuss the limitations of the benefit-risk assessment. Important uncertainties or unknowns should be discussed in this section.

2.4.4 Quantitative Benefit-Risk Analysis

Health Canada has not endorsed a specific quantitative or semi-quantitative methodology, for use in a benefit-risk assessment, at this time. However, this does not preclude the use of these methodologies to support the overall benefit-risk assessment. Include a detailed
description of the methodologies, software used, references and analysed data in an appendix attached to the benefit-risk assessment document. Include and justify results from any quantitative or semi-quantitative methodologies used to perform a benefit-risk assessment on the health product. Briefly justify why a particular methodology was chosen.

2.4.5 Overall Benefit-Risk Analysis

State whether the overall benefit-risk profile has changed.

Discuss if the benefit-risk profile remains positive or has become negative. If the profile has become negative, discuss why it has become negative.

2.5 Final Conclusions and Future Actions

This section summarizes the overall conclusions developed through the benefit-risk analysis. Recommendations and future plans can be discussed in this section.

2.5.1 Conclusions

State the final conclusions regarding the benefit-risk profile of the health product and the rationale behind said conclusions.

2.5.2 Follow-Up Actions

Identify any actions planned or follow-up measures that are intended. Perform an impact analysis.
3 Definitions and Acronyms

**Adverse Event**: 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 temporarily associated with the use of a health product, whether or not considered related to the medicinal product.

**Adverse Reaction**: For the purpose of this guidance document, an adverse reaction refers to a noxious and unintended response to a marketed health product covered.

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

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

**Causality**: The relating of causes to the effects they produce.

**Consultations**: The process of co-ordinating, sharing and including information obtained from various consultants internal or external to the reviewer’s particular bureau.

**Efficacy**: 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**: 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).

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

**Health Products and Food Branch (HPFB)**: The HPFB’s mandate is to take an integrated approach to the management of the risks and benefits to health related products and food by minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.
**Indication for Use:** A statement that describes the limitations for use of a health products, including the disease state, condition(s) or symptom(s) and the target population, if specified, for which the health product is intended and authorized to be used by Health Canada. 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), a Natural Health Product Number (NPN) or a Drug Identification Number for Homeopathic Medicine (DIN-HM) and any related labelling material.

**Market Authorization Holder (MAH):** The MAH is also referred to as Sponsor or Manufacturer. The MAH is the legal entity that holds the Notice of Compliance, the DIN, the NPN, the Homeopathic Medicine Number DIN-HM, the medical device licence number, or that has received approval to initiate clinical trials in Canada.

**Marketed Health Products Directorate (MHPD):** The MHPD works to assure that the Health Products and Food Branch (HPFB) programs take a consistent approach to post-approval safety surveillance, assessment of signals and safety trends and risk communications concerning all regulated marketed health products. Activities of MHPD include: monitoring and collecting adverse reaction and medication incident data; reviewing and analysing marketed health product safety data; conducting risk/benefit assessments of marketed health products; communicating product related risks to healthcare professionals and the public; overview of regulatory advertising activities; providing policies to effectively regulate marketed health products; and active surveillance and drug effectiveness projects.

**Risk:** 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.

AR: Adverse Reaction  
CIOMS: Council for International Organizations of Medical Sciences  
HPFB: Health Products and Food Branch  
IC: Information Component  
MAH: Market Authorization Holder  
SMQ: Standardized MedDRA Queries  
SOC: System, Organ, Class
References

