DRAFT - GUIDANCE DOCUMENT
Submission of Risk Management Plans and Follow-up Commitments

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Presentation Purpose

- Health Canada to present on the elements included in the draft Risk Management Plan guidance document to industry.

- Obtain feedback from stakeholders on the:
  - draft Risk Management Plan Guidance document
  - challenges and opportunities in relation to Risk Management Plans.
  - identification of best practices that will make the Canadian RMP process clearer and easier to understand.

Background

- Notice to Industry was posted in Feb. 2009
- Guidance rather than regulation
- Scope includes drugs, biologics and biotechnology derived products for human use
- Request RMPs in the EU format unless there are special considerations related to medical practice or populations in Canada (e.g., different indication)
- Other formats are acceptable if the document covers essential elements of the EU format

HC RMP Review Activities (1)

Directorate Statistics for RMP Review Activities: Pharmaceuticals and Biologics (Note: Numbers represent RMPs reviewed and not all RMPs received)

RMP	2009-2010	2010-2011	2011-2012	2012-2013	2013-2014
Associated with NDS	16	20	53	60	67
Associated with S/NDS	15	3	8	11	19
Post-market solicited	22	22	24	50	56
Post-market unsolicited	4	3	1	4	8
Total	57	48	86	125	150

HC RMP Review Activities (2)

Directorate Statistics for RMP Review Activities: Pharmaceuticals and Biologics (Note: Numbers represent RMPs reviewed and not all RMPs received)

Recommendations	2009-2010	2010-2011	2011-2012	2012-2013	2013-2014
Labelling Changes	14	14	29	45	45
Additional Risk minimisation measures (request study results, education/training tools, PBRERs)	29	24	42	44	87
Revise and resubmit RMP	16	10	24	57	89
Total	59	48	95	146	221

Stakeholder Engagement Activities

DATE	Title
September 2011	Rx&D/Biotech Canada
November 2011	CAPRA Dinner meeting
October 2012	CAPRA Symposium
October 2013	DIA training & symposium session
October 2013	Rx&D

Evolution of the Guidance

Factors

Legislation

Feedback

Harmonization

Principles

Timeliness

Best Practices

Science-Based

GUIDANCE

Listening to HC reviewers

Generally, there is **significant improvement** since 2007 in the quality of Risk Management Plans submitted.

If a drug is already marketed elsewhere, then there is relevance in the submission of the **post-market** data.

A study designed to evaluate effectiveness of a risk minimization in Europe may not be applicable to the **Canadian context**.

Submitting the most **recent version** available of the Risk Management Plan will minimize unnecessary back and forth and last minutes surprises.

Listening to external stakeholders

Develop a clear, transparent and predictable process **(i.e., guidance document)** in order to better document Health Canada's expectations.

As much as possible an **internationally harmonized** approach should be **adopted**.

When providing recommendations, they should be accompanied with a **rationale** and **timelines** for responding to questions.

"An **integrated inter-directorate** approach for review and approval of RMPs is needed".

RMPs Challenges

- The science of risk management and its framework are a moving target which continue to evolve.

- The international community, including Health Canada, and stakeholders continue to learn about the various aspects of RMPs including:
  - Which risks will need to be included in the RMP
  - What is the most appropriate way to characterize a risk
  - What is the best intervention needed to prevent or mitigate a risk
  - Measuring effectiveness of risk minimization measures and potential burden to the health care system

Consultation: DRAFT Guidance for Industry – Submission of Risk Management Plans and Follow-up Commitments

Comments will be considered in the finalization of the draft guidance. Additionally, this document is part of a broader patient safety risk management framework. In this regard, it is an evolving consultation that will reflect present and future initiatives, such as regulatory, policy and operational changes to support improved patient safety.

The measures outlined in this guidance are effective immediately since they do not impose an obligation but rather provide options for submission to manufacturers.

Background

As an official observer to, and active participant in the International Conference on Harmonisation (ICH), Health Canada is committed to the adoption and implementation of ICH guidances.

In February 2009, Health Canada adopted and implemented the ICH E2E Guideline by publishing the *Notice Regarding Implementation of Risk Management Planning including the adoption of International Conference on Harmonisation (ICH) Guidance Pharmacovigilance Planning - ICH Topic E2E*.

In Canada, the European Union (EU) format represents an acceptable approach to fulfilling requests by Health Canada for Risk Management Plans. However, Health Canada will accept RMPs in other recognized formats provided that they include all the essential elements of the EU RMP.

Objective

The objective of this document is to provide guidance to manufacturers on how to proceed when submitting Risk Management Plans RMPs and follow-up commitments with Health Canada. The principles and practices outlined in the document apply to pharmaceuticals, biologics and biotechnology-derived products for human use, within the scope of ICH E2E. The submission of RMPs for natural health products, medical devices (except when they are part of a combination product submission) and veterinary products are outside the scope of this guidance document.

Consultation Document

To obtain an electronic copy of the document, *DRAFT Guidance for Industry - Submission of Risk Management Plans and Follow-up Commitments*, please send an email to mhpd_dpsc.public@hc-sc.gc.ca with the subject heading **"Comments: Risk Management Plan"** or contact the Marketed Pharmaceuticals and Medical Devices Bureau.

This consultation is open from **March 26, 2014** to **May 26, 2014**.

Distribution List

- Canada's Research-Based Pharmaceutical Companies (Rx&D).
- Canadian Generic Pharmaceutical Association (CGPA)
- Consumer Health Product Canada (CHPC)
- BIOTECHCanada
- Individually to the Biotech and Pharma companies
- Other regulatory jurisdictions (e.g., FDA, EMA, Australia, UK)
- International Society of Pharmacoepidemiology

RMP Guidance Objectives

- Guidance to industry on how to proceed when submitting an RMP in the European Union (EU) format or its equivalent (e.g., United States (US) Risk Evaluation and Mitigation Strategy [REMS]), as well as follow-up commitments and updates.

- Clarification of the way in which the Therapeutic Products Directorate (TPD), the Biologics and Genetic Therapies Directorate (BGTD), and the Marketed Health Products Directorate (MHPD) manage the submission of RMPs and follow-up commitments.

- Define expectations for RMP follow-up commitments.

- Provide an overview of review and approval timelines including deadlines for responding to questions.

Scope

- Pharmaceutical drugs (which includes prescription and non-prescription pharmaceutical drugs).

- Biologics as set out in Schedule D to the Food and Drugs Act (which include biotechnology products, vaccines and fractionated blood products).

- Radiopharmaceutical drugs as set out in Schedule C to the Food and Drugs Act.

- Natural health products, medical devices (except when they are part of a combination product submission and classified in one of the categories outlined above) and veterinary products are outside the scope of this guidance document.

When to file an RMP (1)

- As part of and included in a drug submission [e.g., New Drug Submission (NDS)] seeking issuance of a Notice of Compliance (NOC)

  - New pharmaceutical submissions that include a new active substance (NAS);
  - All biologics and subsequent entry biologics (which include biotechnology products, vaccines and fractionated blood products);
  - All radiopharmaceutical drugs;
  - Any drug that is coming back to the market that was previously withdrawn due to a serious safety issue.

When to file an RMP (2)

- RMPs not part of a drug submission can be requested for, but are not limited to:
  - A marketed drug for which a serious safety issue has been identified;
  - A previously acceptable RMP which has undergone significant changes;

- Generic drugs - on a case by case basis, when it is determined that an RMP is required for the establishment of an adequate risk minimization framework.

RMP Follow-Up Commitments

- A revised RMP.
- A report on specific pharmacovigilance activities (e.g., registry, clinical trial, drug utilization study, or market research study).
- Risk minimization activities (e.g., risk communication, restricted access program, educational or outreach programs).
- Evaluation of effectiveness of risk minimization activities.
- Submission of an Annual Summary Report or its equivalent (PSUR or PBRER).
- Other post-market commitments or updates.

What To Include In Cover letter

- Requested information from Health Canada.
- RMP follow-up commitment.
- An update to a submission - in which case the sponsor/MAH should clearly outline and highlight the changes that have been made.
- Voluntary - unsolicited information in which case the sponsor/MAH should clearly outline the reason for the submission. This can include situations, but are not limited to, where new safety concerns:
  - are identified by the sponsor/MAH which necessitates the submission of an RMP;
  - have resulted in the need for major labelling updates or changes to already implemented additional risk minimization measures in Canada or elsewhere (e.g., EU or FDA);
- Other (please specify).

RMP Format

- The EU format represents an acceptable approach to fulfilling requests by Health Canada for RMPs.

- Other recognized formats are acceptable provided that they include all the essential elements of the EU RMP (i.e., safety specification section, pharmacovigilance and risk minimization activities) as well as any additional information specific to the Canadian context

General Considerations

- Submit the most recent available version of the RMP.
- Incorporate Canadian specific sections, when needed.
- Provide a foreign RMP review and attestation form (if available);
- Include all available post-market data (if marketed in Canada or elsewhere).
- Submit both annotated and non-annotated RMP versions (if revised) and clearly outline the changes that have made.
- Provide a rationale in situations where additional pharmacovigilance (e.g., a drug utilization study, registry) or risk minimization activities (e.g., contraindication, restricted distribution) are proposed or implemented outside of but not in Canada (e.g., Europe) (if applicable).
- Include and reference the most recent version of the Product Monograph.

Canadian Specific Sections (1)

- Include information such as epidemiology of the medical condition(s) or risk factors that reflect the authorized indication(s) in Canada in cases where it varies from the authorized indication(s) in other jurisdictions;
- Reference the latest version of the Canadian Product Monograph (PM);
- Special considerations to genetic or extrinsic factors that are specific to the Canadian population;
- Include information related to Canadian patient exposure (when relevant);
- Provide post-marketing experience in the Canadian context (when available);

Canadian Specific Sections (2)

- Discuss pharmacovigilance activities within the Canadian context; this could involve monitoring of Canadian adverse events from sponsor/MAH's database and reconciliation of such reaction(s) with Health Canada's Vigilance Database.

- In relation to risk minimization and evaluation of effectiveness of risk minimization activities, include information that is applicable to the Canadian context.

- Include appropriate milestones and timelines for reporting on pharmacovigilance and risk minimization activities that are applicable to Canada.

- Canadian specific section(s) can be provided in the form of a Canadian specific RMP or in an addendum to an already prepared EU RMP.

When to Submit RMP updates?

- At the request of Health Canada.

- When the risk management activities are modified, especially as a result of new information that may lead to a significant change to the benefit/risk profile of a drug (i.e., within the safety specification section of the RMP) or as a result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Use of Foreign Reviews

- Reviews from regulatory authorities in the US (FDA) and from the EU's centralized procedure (EMA) should be provided if available.

- The use of reviews from other foreign regulatory authorities may also be considered.

- For more information refer to the *Draft Guidance Document: The Use of Foreign Reviews by Health Canada*.

Who Does What at HC (1)

- Review of RMPs and follow-up commitments is conducted by review bureaus at the MHPD.
- Upon assignment, estimated review time by MHPD is 90 working days.
- For priority review submissions, these timelines may change and are accelerated accordingly.
- Review of a RMP attached to a submission is conducted in parallel with the review in TPD and BGTD, taking into account the deadline for the submission.

Who Does What at HC (2)

- Recommendations stemming from the finalized RMP review which include RMP follow-up commitments are communicated to the manufacturer by either MHPD or pre-market bureau.

- In general for RMPs attached to a submission pre-market bureau is the point of contact. For RMPs outside of a submission, MHPD is the point of contact.

- Timelines to respond to Health Canada may vary depending on the safety issue being managed. The manufacturer is generally provided with a minimum of 15 days to respond.

Location & Contact Informatio

- **Office of Submissions and Intellectual Property (OSIP)**
  Therapeutic Products Directorate
  Health Canada
  Postal Locator 0201A1
  101 Tunney's Pasture Driveway
  Ottawa, ON K1A 0K9

- For regulatory correspondence related to RMPs outside of a submission or follow-up commitments use the above address, but include it to the attention of the relevant review bureau (i.e. MBBNHPB or MPMDB) at the MHPD.

- For inquiries related to electronic format, please contact Health Canada using the following e-mail address: E-mail: ereview@hc-sc.gc.ca

Conclusions

- The science of risk management is comparatively new and best practices continue to be developed.

- As we develop, we will continue to follow certain principles
  - Work collaboratively to establish best practices
  - Be tolerant and adaptive to change as new information emerges
  - Minimize unnecessary variation by creating processes that are consistent, predictable and easy to understand.