Guidance Document - Submission of Risk Management Plans and Follow-up Commitments

Effective Date: June 26, 2015

Health Canada is the federal department responsible for helping the people of Canada maintain and improve their health. We assess the safety of drugs and many consumer products, help improve the safety of food, and provide information to Canadians to help them make healthy decisions. We provide health services to First Nations people and to Inuit communities. We work with the provinces to ensure our health care system serves the needs of Canadians.

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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 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 program 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 Policy Objectives

Health Canada has adopted and integrated the use of Risk Management Plans (RMPs) and the International Conference on Harmonization (ICH) E2E Guideline into the regulatory review of drugs in Canada in order to:

- Support a life cycle approach to drug vigilance;
- Enhance the quality of Health Canada's regulatory assessments;
- Support Canadians' timely access to safe, efficacious and high quality drugs;
- Support ongoing evaluation of information that could have an impact on the benefit-risk profile of health products and;
- Align drug vigilance with international best practices.

1.2 Scope and Application

This document provides the sponsor/market authorization holder (MAH) with guidance on how to proceed when submitting a Canadian RMP in the European Union (EU) format or other recognized formats (e.g., United States (US) Risk Evaluation and Mitigation Strategy [REMS]), as well as RMP follow-up commitments and updates with Health Canada.

Additionally, the current document will:

- Provide clarification to sponsor/MAH of the way in which the Therapeutic Products Directorate (TPD), the Biologics and Genetic Therapies Directorate (BGTD), the Natural and Non-prescription Health Products Directorate (NNHPD) and the Marketed Health Products Directorate (MHPD) manage the submission of RMPs and follow-up commitments;
- Define expectations for RMP follow-up commitments;
- Provide the sponsor/MAH with an overview of review and approval timelines including deadlines for responding to questions.

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

- 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.

The submission of RMPs for 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.

1.3 Background

The decision to approve a drug is based on it having a satisfactory balance of benefits and risks within the conditions specified in the product labeling. This decision is based on the information available at the time of approval. The knowledge related to the safety profile of the drug can change over time through expanded use in terms of patient

characteristics and the number of patients exposed. In particular, during the early post-marketing period the drug might be used in settings different from those studied in clinical trials and a much larger population might be exposed in a relatively short timeframe.

In 2004, the ICH released the *Pharmacovigilance Planning E2E Guideline*. The ICH E2E Guideline provides instruction with respect to the further characterization of important identified risks of drugs, important potential risks and missing information. ICH E2E defines two basic parts of an RMP: the safety specification section and the pharmacovigilance plan. It does not include risk minimization. However, it was acknowledged at the time of development of ICH E2E that risk minimization is an integral part of risk management planning.

In 2005 and in compliance with the European legislation, the EU announced that the primary document and process for RMPs adheres to the principles outlined in the ICH E2E Guideline. At that time the basic EU RMP structure included three main sections: the safety specification section, the pharmacovigilance activities and risk minimization plan. In 2012, new EU pharmacovigilance legislation was announced which strengthened procedures for the submission of RMPs to the Agency and was accompanied with modifications to the basic EU RMP structure.

In 2007, the US Food and Drug Administration Amendments Act (FDAAA) gave the FDA authority to require sponsors/MAHs to develop and comply with Risk Evaluation and Mitigation Strategies (REMS). REMS are similar in concept to the EU risk minimization activities.

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 the notice, Health Canada advised that the EU format represents an acceptable approach to fulfilling requests by Health Canada for RMPs. However, if there are special considerations related to medical practice or populations in Canada, the sponsor/MAH should also provide a Canadian context to the submitted RMP. Health Canada further advised that other recognized formats are accepted (i.e. REMS), as long as they cover the essential elements outlined in the EU RMP format (refer to section **3.2** for more detail).

2 Definitions and Acronyms

Additional Risk Minimization Activity
An intervention intended to prevent or reduce the probability of an undesirable outcome, or reduce its severity should it occur, which is in addition to the routine risk minimization activities. Examples include drug administration training or additional educational material.

Additional Pharmacovigilance Activities
For products for which special concerns have arisen, additional activities designed to address these safety concerns should be considered (e.g., safety studies).

Data Package
For the purposes of this document, data package is: a formal submission or application to a regulatory authority in order to obtain a regulatory decision or to maintain regulatory status for a drug. In Canada, this includes data as per the Food and Drug Regulations or other information filed for review by Health Canada (e.g. Risk Management Plans filed independently of a submission, Periodic Safety Update Reports).

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

International Conference on Harmonisation (ICH)
The International Conference on Harmonisation is a joint regulatory-industry initiative pertaining to the international harmonisation of regulatory requirements for drug products. The parties in ICH represent the regulatory bodies and research-based industry in three regions (North America, Europe and Japan). Most new medicines are currently developed in these regions.

ICH E2E
E2E, the ICH Guidance on Pharmacovigilance Planning, was finalized in November 2004. The guideline is intended to aid in the planning of pharmacovigilance activities, especially in preparation for the early post-marketing period of a new drug. It focuses primarily on specific aspects of a Safety Specification and Pharmacovigilance Plan that may be submitted at the time of an application for market authorization.

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

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

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

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

Risk Management Plan (RMP)
A document that describes a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks related to drug products, and the assessment of the effectiveness of those interventions (adopted from the European Medicines Agency definition of a Risk Management System).

Risk Minimization Activity
Risk minimization activities are interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur. These measures may include warnings in the label or minimization activities beyond routine, such as health care provider educational material.

Routine Pharmacovigilance activities
For products for which no special concerns have arisen, routine pharmacovigilance activities are sufficient for post-approval safety monitoring. This can include monitoring of the safety profile of the product through signal detection activities and preparation of reports for regulatory authorities (i.e., PSURs).

Routine Risk Minimization Activities
Routine risk minimization activities apply to all medicinal products and relate to standard activities such as product labelling and limitations on drug pack size.

Safety Specification
The safety specification is a summary of the important identified risks of a medicinal product, important potential risks, and missing information. The safety specification should also address the populations potentially at risk (where the drug is likely to be used), and outstanding safety questions which warrant further investigation to refine understanding of the benefit-risk profile during the post-authorization period.

Serious Adverse Drug Reaction

"Serious adverse drug reaction" as defined in the Food and Drug Regulations means a noxious and unintended response to a drug that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death.

3 Procedures

3.1 When to file a Risk Management Plan with Health Canada

RMPs are submitted to Health Canada either (refer to section **3.9** for more detail):

- As part of and included in a drug submission [e.g., New Drug Submission (NDS) or Supplemental New Drug Submission (S/NDS)] seeking issuance of a Notice of Compliance (NOC) ;
- Not part of a drug submission (e.g., not linked to a NDS).

RMPs should be included in a drug submission in the following circumstances, but not limited to:

- New pharmaceutical submissions that include a new active substances (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;
- Drugs with a significant change in indication;
- Drugs with the designation "Extraordinary Use" (EU) (refer to **Appendix 2** for more detail).

If stakeholders have questions regarding whether or not an RMP should be submitted to Health Canada, they are encouraged to start dialogue early well in advance of the submission process (i.e. pre-submission meetings - refer to section 3.9.1 for more detail).

RMPs not linked to a NDS or S/NDS can be requested for, but not limited to:

- A marketed drug for which a serious safety issue has been identified;
- A previously acceptable RMP which has undergone significant changes;
- Drugs new to a class for which a serious or potentially serious safety risk has been identified to another member of the class.

RMPs (or sections of the RMP) are requested by Health Canada for generic drugs:

- When it is determined that an RMP is required for the establishment of an adequate risk minimization framework. As an example this can include situations where additional risk minimization activities (e.g., restricted distribution program, designated laboratory tests, distribution of educational materials) are in place for the innovator product. Generic manufacturers should refer to the innovator Canadian Product Monograph to identify if additional risk minimization measures have been implemented for the innovator product.
- As a result of safety issues associated with a generic drug.

Health Canada will inform generic sponsors/MAHs for the requirement of an RMP or the need to implement additional risk minimization activities already in place for the innovator product in addition to timelines to do so.

Additionally, for a marketed drug, if the MAH identifies that there has been a significant change to what is known about the benefits, harms, or uncertainties associated with the drug an RMP or an update to the RMP should be submitted to Health Canada (refer to section **3.7** for more detail). This applies to cases where no previous Canadian RMP exists or when an update is needed to a previously acceptable RMP. When a generic drug exists for the innovator product affected, Health Canada will notify the generic manufacturer requesting revision or submission of a generic product RMP as appropriate.

RMPs can also be requested by Health Canada as part of an ongoing review or other situations in order to support informed regulatory decision making about the drug. In general the timeline for submission of RMPs once requested by Health Canada is 30 calendar days.

3.2 Acceptable Risk Management Plan Format

In Canada, the EU format represents an acceptable approach to fulfilling requests by Health Canada for RMPs. However, Health Canada will accept RMPs in other recognized formats provided that they include all the essential elements of the EU RMP (i.e., safety specification section, pharmacovigilance activities, risk minimization activities, and evaluating effectiveness of risk minimization measures) as well as any additional information specific to the Canadian context (refer to section **3.8** for more information).

3.3 General Considerations

An RMP is a dynamic stand-alone document reflecting both emerging known and unknown safety data (i.e., clinical and non-clinical) that should be updated throughout the drug's life-cycle (refer to section 3.7 for more detail) upon discussion and agreement between Health Canada and the sponsors/MAHs. Sponsors/MAHs are encouraged to consider the following in their submission of RMPs and follow-up commitments related to previous RMPs:

- Submit the most recent version available of the Canadian RMP at the time of initial submission with Health Canada. Additionally, if for example an EU-RMP was submitted to Health Canada as the Canadian RMP at the time of initial submission and a revised EU-RMP were to become available later during the regulatory review process, the sponsor/MAH should notify Health Canada and is encouraged to proactively file the revised EU-RMP and Canadian specific addendum (if necessary);
- Incorporate Canadian specific sections, when needed (refer to section **3.8** for more detail);
- Provide a foreign RMP review and attestation form (if available) (refer to section 3.5 for more detail);
- Include available post-market data (if marketed in Canada or elsewhere). For example, if there is a submission in Canada for a drug that is already marketed elsewhere (e.g., Europe), there will be value in including the market experience of that drug in the RMP;
- Submit both clean and track change versions of the RMP and addendum to the RMP (if revised) and clearly outline the major changes that have been made since the last submitted version (refer to section 3.6 for more detail);
- 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 in major jurisdictions (e.g., Europe or US) but not in Canada. This information can be included in an appendix to the RMP or Canadian addendum;
- Reference the most recent version of the Canadian Product Monograph.

3.4 Submission

As per guidance documents posted on the Health Canada Web site, there are currently two acceptable formats for filing RMPs or follow-up commitments:

- Please refer to *Draft Guidance Document: Preparation of Drug Regulatory Activities in Electronic Common Technical Document (eCTD)* for further information concerning Regulatory activities/submissions in eCTD format.
- If RMPs or follow-up commitments are not submitted in eCTD format, sponsors/MAHs should submit them in electronic non-eCTD format using the structure template recommended in "Appendix D: Common

Technical Document (CTD) Format" of the guidance document *Preparation of Drug Regulatory Activities in the Common Technical Document (CTD) Format*.

Sponsors/MAHs should refer to the Health Canada's *Management of Drug Submissions Guidance* document for general procedures on how to file submissions.

3.5 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 at time of initial submission of the data package to Health Canada. For RMPs attached to a submission, if the foreign RMP review is not available at the time of initial submission but becomes available later during the regulatory review period, it can be submitted as unsolicited information.

The use of reviews from other foreign regulatory authorities may also be considered [e.g. Switzerland's Swissmedic; Australia's Therapeutic Goods Administration (TGA); and Singapore's Health Sciences Authority (HSA)].

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

For more information on the use of foreign reviews, please refer to the *Draft Guidance Document: The Use of Foreign Reviews by Health Canada*.

3.6 Cover Letter and Note to Reviewer

All RMPs, follow-up commitments and updates should be accompanied by a cover letter and a Note to reviewer. If the RMP is included with a NDS, the NDS cover letter should make reference to the RMP.

The cover letter should indicate the submission type (e.g., RMP update). Scientific information related to the reason for submission or summary of changes that have been made to the RMP should be included in Module 1.07 (Note to reviewer- refer to *Draft Guidance Document: Preparation of Drug Regulatory Activities in Electronic Common Technical Document (eCTD)* for more information). For example the cover letter or Note to reviewer can include the following information:

- Requested information from Health Canada;
- RMP follow-up commitment;
- An RMP update where changes are clearly outlined;
- Voluntary – submission of unsolicited information in which case the reason for the submission should be clearly outlined. This can include situations where, but not limited to:
    - New safety concerns are identified by the sponsor/MAH which necessitates the submission of an RMP;
    - Modifications to implemented risk minimization or pharmacovigilance activities.
- Other (please specify).

3.7 Risk Management Plan Updates

The sponsor/MAH should perform the required pharmacovigilance and risk minimization activities detailed in the Canadian RMP approved by Health Canada, as well as any agreed upon activities detailed in subsequent RMP updates. Moreover, it is the responsibility of the sponsor/MAH to monitor the safety profile of the drug and to update and submit an update to the RMP if there is a significant change to its benefits, harms or uncertainties.

Situations where an RMP update will normally be expected include, but not limited to:

- Whenever the risk management activities are modified as a result of new information that has come to the attention of the sponsor/MAH that may lead to a significant change to the benefits, harms or uncertainties of a drug in the Canadian context (e.g., identification of serious safety concerns which will require implementation of additional pharmacovigilance activities and/or changes to the risk minimization activities);
- At the request of Health Canada;
- Submission of final study results impacting the RMP (e.g., confirmation of a safety risk that will require modifications to various parts of the RMP).

The need for an RMP update can be discussed with Health Canada as appropriate. In general timeline for submission of RMPs once requested by Health Canada is 30 calendar days.

Each RMP update should have a distinct version number and date. When any part of the RMP is revised, the revision date should be reflected as the "Last Revised" date which is when the RMP is considered final. A new RMP version number should be assigned each time any parts/modules are updated. Additionally, both clean and track change versions should be submitted to Health Canada along with the cover letter and Note to reviewer detailing the changes since the last submitted Canadian version (refer to section **3.6** for more detail).

3.8 Canadian Specific Sections

If no Canadian specific considerations are required, an EU RMP or other recognized formats (refer to section 3.2 for more detail) is acceptable for submission in Canada. However, although risk management planning has become a global activity, regional differences and the settings for the use of a drug can vary from country to country which will justify flexibility within standardization. Below are examples of special considerations related to medical practice or populations in Canada that should be considered, if applicable, when submitting an RMP or follow-up commitments:

- Include information such as epidemiology of the medical condition(s) or risk factors that reflect the authorized indication(s) in Canada [e.g., in cases where it varies from the authorized indication(s) in other major jurisdictions (i.e., Europe, US) or when the drug is intended to be used in a small group of patients in Canada];
- Reference the latest version of the Canadian Product Monograph;
- Include special considerations to genetic or extrinsic factors that are specific to the Canadian population. For example a number of rare hereditary disorders are specific to regions in Quebec such as autosomal recessive spastic ataxia of Charlevoix-Saguenay;
- Include information related to Canadian patient exposure;
- Provide post-authorization experience in Canada and/or worldwide. For example, if a drug has been marketed outside of Canada for a period of time knowledge has been collected in relation to emerging risks that were not identified in clinical trials. A summary of such information should be submitted to Health Canada;
- 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 additional 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 or RMP in other recognized formats (refer to section **3.2** for more detail).

3.9 Review of Risk Management Plans and follow-up commitments

The review of RMPs and follow-up commitments is conducted by review bureaus at the MHPD. This includes the Marketed Pharmaceutical and Medical Devices Bureau (MPMDB) and the Marketed Biologicals, Biotechnology and Natural Health Products Bureau (MBBNHPB). Upon assignment of an RMP to a reviewer, the estimated review time by MHPD of an RMP is 90 working days. This target timeline applies to all submission types (e.g., NDS, SNDS, etc.). For priority review submissions, the sponsor will be provided with priority review timelines.

3.9.1 Review of Risk Management Plans that are part of a drug submission

Sponsors wishing to file a submission with Health Canada are encouraged to identify if an RMP is necessary by referring to the criteria outlined in section **3.1**. Sponsors are encouraged to request a pre-submission meeting to discuss all aspects of their submission including RMPs. Representatives from the MHPD who are present at the pre-submission meetings can provide appropriate guidance on the content and format of the RMP to be submitted. A draft RMP may be included in the data package for a pre-submission meeting. Alternatively, an outline of the RMP or any potential questions related to the RMP may be discussed at a pre-submission meeting.

Regulatory correspondence for RMPs attached to a submission should include reference to the Drug Submission Tracking System (DSTS) control number. Sponsors should also refer to the Health Canada guidance document titled *Management of Drug Submissions* for instructions on how to request pre-submission meetings. Sponsors should forward their pre-submission meeting requests to the appropriate Directorate (Office) located within Health Canada, please refer to **Appendix 1** for relevant contact information.

For products for which an RMP is expected (as outlined in section **3.1**), the submission will be screened for its inclusion or a rationale as to why it was not included. If an RMP was not provided, a screening request via clarifax will be sent to the sponsor to provide the RMP or a rationale as to why it was not included.

After the submission is considered acceptable to proceed for review, the RMP will be forwarded to the MHPD for review. The RMP review is conducted in parallel with the review in the pre-market bureaus, taking into account the deadline for the submission to ensure that there are no delays.

During the parallel review process information is exchanged between pre- and post- market review bureaus in order to obtain context in relation to the information that is included in the RMP in addition to, assessing whether the RMP sections are described appropriately (e.g., identify if all important potential and identified risks described in the submission under review by the pre-market bureaus have also been addressed in the safety specification section of the RMP). Additionally, the MHPD will consult with the pre-market bureaus regarding issues identified in the RMP review, including any deficiencies that may need to be addressed, and communicate outcomes of the RMP review with the pre-market review divisions. The recommendations and/or deficiencies provided by the MHPD may be included in the respective pre-market submission review processes

(i.e., clarifax) or taken into account by the pre-market bureaus in their final decision as to whether or not an NOC ought to be issued.

The recommendations stemming from the finalized RMP review (e.g., RMP is acceptable or not) are communicated to the sponsor either prior to or within 60 days to issuance of the final decision by the pre-market bureaus (e.g., NOC). The Health Canada RMP review report can be shared with the sponsor upon request.

3.9.2 Review of Risk Management Plans not "included in" OR "part of" a submission and follow-up commitments

The process detailed below provides an overview of how RMPs not submitted in conjunction with a submission (e.g., NDS) and follow-up commitments are managed by Health Canada. Examples of RMPs submitted to Health Canada outside of a drug submission can include the following, but not limited to:

- An RMP for a marketed drug in Canada for which a new emerging and/ or serious post market safety issue is identified.
- An RMP for a marketed drug in Canada for which a new serious safety risk is identified for a similar product in the class.

For RMPs submitted to Health Canada outside of a drug submission, a request letter for them is communicated to the market authorization holder.

Following the review of a RMP, Health Canada may recommend a number of RMP follow-up commitments that are communicated to MAH which can include, but are not limited to, the following:

- An updated RMP;
- A report on specific pharmacovigilance activities (e.g., registry, clinical trial, drug utilization study, or market research study);
- Risk minimization activities (e.g., labelling, risk communication, restricted access program, educational or outreach programs);
- Evaluation of the impact of routine and/or additional risk minimization activities as applicable (e.g., conducting a drug utilization study or a market research to monitor if information included in the product monograph is being applied by health care professionals and patients, parameters to measure undue burden on patients or the healthcare system);
- Submission of an Annual Summary Report or its equivalent (PSUR or PBRER).

In relation to the process, during the review of an RMP or follow-up commitments, the MHPD may communicate with the MAH to clarify on RMP related issues. Responses to these clarification requests should be sent to the attention of the MHPD as per instructions provided in section **3.10** and in **Appendix 1** below. Upon completion of the review of the RMP or follow-up commitments, the MHPD will communicate with the sponsor/MAH to inform on the approval of the document or on deficiencies that have been identified by the MHPD. If deficiencies have been identified by the MHPD, timelines for response by the MAH will be included in the feedback letter sent by MHPD. The timelines may vary depending on the safety issue being managed. The MAH is generally provided with a minimum of 15 to 30 calendar days to respond, however these timelines are subject to change following a discussion between Health Canada and the MAH. The Health Canada RMP

review report can be shared with the MAH upon request. Additionally, for RMPs that are not attached to a submission they can be tracked in the Drug Submission Tracking System (DSTS).

In situations where there has been an addition or a revision to the RMP follow-up commitments, the post-approval commitment table within Module I of the RMP should be updated. A copy of the table may be requested by MHPD for record's management. The review outcomes conducted by the MHPD are also shared with the appropriate bureau in the TPD, NNHPD or the BGTD.

3.10 Location

Sponsors/MAHs are requested to submit RMPs and follow-up commitments to the Office of Submissions and Intellectual Property (OSIP).

Office of Submissions and Intellectual Property (OSIP)
Therapeutic Products Directorate
Health Canada
Postal Locator 0201A1
101 Tunney's Pasture Driveway
Ottawa, Ontario
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: ereview@hc-sc.gc.ca

3.11 Status Requests

In an effort to streamline administrative processes and expedite drug submission reviews, regulatory project managers are assigned to each review bureau in TPD, NNHPD and MHPD, and senior regulatory affairs officers to each submission in BGTD. The regulatory project managers and officers will serve as the primary points of contact between the review bureaus and the sponsor/MAH.

Sponsors/MAHs with questions regarding their submissions should contact (refer to **Appendix 1** for specific contact information):

- The relevant Office of Regulatory Affairs in BGTD or the regulatory project manager servicing the relevant review division in TPD/NNHPD for RMPs attached to a BGTD or TPD/NNHPD submission respectively (e.g., New Drug Submission);
- The regulatory project manager in MHPD for RMPs outside of a TPD/NNHPD or BGTD submission or follow-up commitment.

Appendix 1 - Contact Information

Biologics and Genetic Therapies Directorate
Office of Regulatory Affairs
Health Products and Food Branch
Health Canada
Address Locator 0701A
Tunney's Pasture Driveway,
Ottawa, Ontario
K1A 0K9

E-mail: dpbtg_ora@hc-sc.gc.ca
Facsimile: 613-946-9520

Marketed Biologicals, Biotechnology and Natural Health Products Bureau
Regulatory Project Management Section
Health Canada
Address Locator 0702L
200 Tunney’s Pasture Driveway
Ottawa, Ontario
K1A 0K9

E-mail: MBBNHPB_RPM@hc-sc.gc.ca
Facsimile: 613-954-2354

Marketed Pharmaceuticals and Medical Devices Bureau
Regulatory Project Management Section
Health Canada
Address Locator 0702L
200 Tunney’s Pasture Driveway
Ottawa, Ontario
K1A 0K9

E-mail: MPMDB_RPM@hc-sc.gc.ca
Facsimile: (613) 960-9754

Natural and Non-prescription Health Products Directorate
Regulatory Project Manager
Non-prescription Drug Evaluation Division
Qualicum Towers, Tower A
Health Canada
Address Locator 3302A
2936 Baseline Road,
Ottawa, ON
K1A 0K9

Facsimile: 613-946-9514

Therapeutic Products Directorate
Regulatory Project Management Division, servicing TPD
Health Canada
Address Locator 0202D2
101Tunney's Pasture Driveway,
Ottawa, Ontario
K1A 1B9

E-mail: RPM_Division-GRP_Division@hc-sc.gc.ca
Facsimile: 613-952-9310

Appendix 2 - List of relevant guidance documents

Sponsors/MAHs should refer to the most up-to-date versions of the following Guidance documents. This list is provided as a starting point to help sponsors/MAHs, and is not exhaustive.

Health Canada Guidance Documents and Notices

- Guidance for Industry: Management of Drug Submissions
- Draft Guidance Document: Preparation of Drug Regulatory Activities in Electronic Common Technical Document (eCTD)
- Guidance Document: Creation of the Canadian Module 1 Backbone
- Canadian Module 1 Schema Version 2.2
- Preparation of Drug Regulatory Activities in the Common Technical Document (CTD) Format
- Guidance for Industry: Product Monograph
- Guidance for Industry: Product Monograph, Appendix E - Product Monograph Template - Standard
- Fees for the Review of Drug Submissions and Applications
- Notice: Implementation of Risk Management Planning including the adoption of International
- Conference on Harmonisation (ICH) Guidance Pharmacovigilance Planning - ICH Topic E2E
- Reporting Adverse Reactions to Marketed Health Products
- Notice: Adoption of the International Conference on Harmonisation (ICH) Guidance on Periodic Benefit Risk Evaluation Report - ICH Topic E2C(R2)
- Draft Guidance Document – The Use of Foreign Reviews by Health Canada
- Guidance Document – Submission and Information Requirements for Extraordinary Use New Drugs (EUNDs).

International Conference on Harmonization (ICH) Guidance Documents

- ICH E2E: ICH Harmonized Tripartite Guideline: Pharmacovigilance Planning E2E
- ICH E2C: Periodic Safety Update Reports (PSURs)
- ICH E2C-R2: Periodic Benefit-Risk Evaluation Reports (PBRERs)

European Medicines Agency Guidelines

- Guideline on Good Pharmacovigilance Practices: Module V – Risk Management Systems
- Guidance on Format of the Risk Management Plan (Plan) in the EU – in integrated format

Food and Drug Administration Guidance

- Guidance for Industry: Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications