Health Canada Question and Answer Document regarding the Implementation of Risk Management Planning

1. What is a Risk Management System and what is its role in product regulation in Canada?

A Risk Management System is defined as "a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products, and the assessment of effectiveness of those interventions"[1]. Health Canada is considering a Risk Management System approach similar to the European model, which includes: (1) a Safety Specification, which is a summary of the known important safety information about the health product and is a means to identify gaps in knowledge; (2) a Pharmacovigilance Plan, which is based on the Safety Specification and identifies and characterizes known or potential safety concerns; and (3) a Risk Minimization plan (RMinP), which provides proposals on how to minimize any identified or potential safety risks. For the purposes of Health Canada's interim approach, the proposed term will be Risk Management Planning (RMP), based on our proposal to use the European Union Risk Management Plan template.

Risk Management Planning will not reduce the scientific standards for market authorization of therapeutic products, nor will it replace the precautionary approach that is taken to managing risks associated with those products[2]. On the contrary, implementation of Risk Management Planning will further strengthen the rigour of post-market surveillance, allowing for earlier identification of risks associated with therapeutic products and earlier interventions to minimize those risks.

While drug manufacturers assume ultimate responsibility for monitoring their products post-authorization to ensure that a drug's benefits continue to outweigh its risks, Health Canada has a regulatory mandate to intervene and protect the public from exposure to harm when scientific evidence suggests that such harm exists. Implementation of Risk Management Planning (RMP) will not lessen Health Canada's regulatory responsibility in any way. RMPs provide for a more proactive means of managing risks associated with products, reflecting the fact that the responsibility of the manufacturer continues after a product is marketed.

2. Will implementation of Risk Management Planning lower the standard for getting a drug to market?

Strengthening the post-market requirements for drugs through implementation of Risk Management Planning in no way decreases pre-market requirements. Risk Management Planning was developed in response to perceived limitations in the old "point-in-time" approach

---

1 The European Medicines Agency Web site: http://www.emea.europa.eu/htms/human/raguidelines/pharmacovigilance.htm

2 Health Canada Issue Identification Paper http://www.hc-sc.gc.ca/ewh-semt/contaminants/person/impact/consultation/draft-ebauche/iip-dde_app-annc-eng.php

to drug regulation that led to withdrawals from the market of high-profile drugs for safety reasons.

The intent of Risk Management Planning is to identify safety issues early in a product's lifecycle, to develop methods to quantify and assess that risk and to then put in place risk management measures that will be monitored and evaluated to determine their effectiveness in minimizing the risk and to allow for identification of new risks that may only be observed in the post-market setting. For instance, a company may identify in a safety specification that they have not tested their product in clinical trials in geriatric patients. The pharmacovigilance plan could propose a prospective case-control study that follows geriatric patients through time to determine if there are any particular adverse events that are observed in the group of patients who receive the drug. If the study identified a serious adverse event that occurred in geriatric patients, the risk minimization activities could address how to minimize that risk, potentially including a contraindication to the use of that product in geriatric patients. The company would then be expected to look at a drug prescription database to determine if geriatric patients are being prescribed that product despite the contraindication and, if so, to come up with another approach to mitigate the risk. Implementation of RMP is, therefore, an increase in the rigour with which companies and the government regulate products.

3. What are Health Canada's current activities that relate to Product Vigilance (PV) and Risk Management?

Health Canada currently engages in risk management by reviewing:

- Applications for the conduct of clinical trials in Canada to ensure that the rights of the participants are respected and that potential risks are mitigated;
- Adverse drug reactions that happen during clinical trials in Canada;
- Data submitted to Health Canada in drug submissions, including product information (labels, product monographs, package leaflets) to determine if the information requires specific risk management measures;
- Adverse reaction reports and published scientific and medical literature to identify new risks; and
- Periodic safety update reports, which are a tool for companies to conduct systematic analyses of safety data and systematically document their vigilance activities and interactions with federal regulatory agencies on a regular basis.

Health Canada also:

- Works with drug manufacturers and health professionals to develop risk management tools and select risk mitigation strategies; and
- Oversees risk communications to health professionals, caregivers and patients;
- Consults with an Expert Advisory Committee on Vigilance of Health Products.

The risk management activities of manufacturers reviewed by Health Canada include:

- Proposals for conducting post-market studies to further characterize risks associated with a drug;
- Creating product labels, product monographs, and package inserts that are accurate;
- Quality monitoring of biologics through a lot-release program;
- Proposals for controlling distribution or creating registries; and
- Communicating new risk information to health professionals and patients.

4. How does Risk Management Planning (RMP) fit in with other Product Vigilance (PV) and RMP activities already in place?

The implementation of Risk Management Planning is intended to fit into a broader Product Vigilance framework that is being established at Health Canada. The intent of this initiative is to provide a standardized and systematic integrated risk management approach, including the use of regulatory tools to support and enhance health Product Vigilance review activities for pre- and post-authorization of health products. One purpose of the interim implementation is to investigate how Risk Management planning will integrate with ongoing and future pharmacovigilance activities.

5. What is the relationship of Risk Management Planning (RMP) to initiatives to modernize the *Food and Drugs Act* and *Regulations*?

The goal of the modernization of the regulatory framework for health products is to develop a modern, integrated approach to the regulation of pharmaceuticals and biologics that can be implemented throughout the life cycle of these products. The Project is an initiative under the Health Products and Food Branch's *Blueprint for Renewal*, a long-term policy framework for improving the regulatory system for health products and food. Risk Management Planning is intended to be part of this framework that will be established by Health Canada. This framework recognizes that the information regarding product safety is established at the time of market authorization based on the results of clinical trials that may not include all types of patients to whom the product will be given once it is on the market. Risk Management Planning is recognized as a key component of the life cycle approach to health product regulation.

6. Does Risk Management Planning (RMP) relate to Health Canada's Food and Consumer Safety Action Plan (FCSAP)?

The Food and Consumer Safety Action Plan (FCSAP) is an integrated, risk-based action plan that is premised on three key pillars: active prevention, targeted oversight and rapid response. Risk Management Planning is recognized as a key component of the FCSAP for health products and links to the three key pillars. RMP is a proactive method to identify early the risks associated with marketed health products and develop methods to maximize product benefit while minimizing risk. The implementation of RMP enables the regulator to have oversight of ongoing risk management activities and makes companies accountable for reporting on the ongoing need for risk management. In addition, ongoing pharmacovigilance and risk management activities by industry and regular reporting to the regulator will enable rapid responses to identified risks.

7. Does Canada have the regulatory authority to compel submission of these Risk Management Plans?

Currently, Health Canada will be requesting submission of Risk Management Plans on a voluntary basis. There has been an international trend to formally incorporate such plans through legislation and regulations. It is anticipated that modernization of Canadian legislation and regulations to adopt a product life cycle approach to pharmaceuticals would include the ability to require Risk Management Plans for certain products.

8. For which products will Risk Management Planning (RMP) be requested during the interim implementation?

The scope of the interim implementation includes International Conference on Harmonisation (ICH) products, is to include drugs, biologics and biotechnology-derived products. Natural Health Products, Medical Devices and Veterinary Products are currently outside of the scope. Part of the intent of the interim implementation is to determine whether Health Canada should implement Risk Management Plans across all health product lines.

9. What approach have other regulators taken to Risk Management Planning?

In both Europe and the United States, regulators made the decision to implement a Risk Management Planning component as well as the E2E document on Pharmacovigilance Planning. In Europe, the European Union (EU) implemented the Guideline on Risk Management Systems for Medicinal Products for Human Use including the EU-RMP in November of 2005. In the United States the Food and Drug Administration (US FDA) published three separate guidance documents on Premarketing Risk Assessment, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment and Development, and Use of Risk Minimization Action Plans (RiskMAPs), also in 2005. Further to recent updates to the *Food and Drugs Act* (the *Food and Drugs Amendments Act* - FDAAA), the US FDA is now requiring Risk Evaluation and Mitigation Strategies (REMs) for certain products with "exceptional circumstances" although these exceptional circumstances have not yet been defined.

10. What is the International Conference on Harmonisation?

The *International Conference on Harmonisation (ICH)*[3] is a project that brings together regulatory bodies and research-based industry in the three regions (US, Europe, and Japan) where most new medicines are currently developed. The purpose of ICH is to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines through the development and implementation of harmonized technical guidelines and standards for the development, registration and surveillance of pharmaceutical products.

The six parties to ICH are:
- the European Commission, representing the EU;
- the European Federation of Pharmaceutical Industries and Associations (EFPIA);
- the Ministry of Health, Labour and Welfare of Japan (MHLWP);

[3] Full name: *International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use*

- the Japanese Pharmaceutical Manufacturers Association (JPMA);
- the United States Food and Drug Administration (FDA) and
- the Pharmaceutical Research and Manufacturers of America (PhRMA).

In addition there are three ICH observers:

- the World Health Organisation (WHO);
- The European Free Trade Area (EFTA), represented by the Swiss Authority Swissmedic; and
- Canada represented by the Canadian authority, Health Canada.

In 2004, ICH endorsed the Pharmacovigilance planning Guideline (known as topic "E2E"), which is intended to aid in the planning of pharmacovigilance activities, especially in preparation for the early postmarketing period of a new drug. The scope of E2E includes new medicines and significant modifications to existing medicines (for example, a new dosage form or a new route of administration). As an observer to ICH, Health Canada has committed to implementation of ICH guidelines.