Questions and Answers Regarding the Implementation of a Risk-Prioritized Periodic Safety Update Report Regulatory Review Pilot (PSUR-RRP) at Health Canada

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1. What is a Periodic Safety Update Report (PSUR) and how is this tool used to enhance pharmacovigilance (PV) activities at Health Canada?

A PSUR is intended to provide an update of the worldwide safety experience of a medicinal product to international health regulatory authorities at defined intervals post-authorization.

The PSUR can be an important source for the identification of new safety signals, a means of determining changes in the benefit-risk profile, an effective means of risk communication to regulatory authorities and an indicator for the need for risk management initiatives, as well as a tracking mechanism for monitoring the effectiveness of such initiatives. For these reasons, the PSUR can be an important pharmacovigilance (PV) tool at Health Canada.

2. What role does the PSUR-RRP have in product regulation in Canada?

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. PSURs provide for a

more proactive means of identifying safety concerns associated with products throughout their lifecycle, reflecting the fact that the responsibility of the manufacturer continues after a product is marketed.

Implementation of a risk-prioritized PSUR-RRP will allow Health Canada to focus and target more efficiently the review and management of PSURs. In addition, it will further strengthen the rigor of post-market surveillance, allowing for earlier identification and monitoring (i.e. lifecycle management) of worldwide safety issues associated with therapeutic products and earlier interventions to minimize them.

3. How does the voluntary systematic risk-prioritized PSUR-RRP fit with other pharmacovigilance (PV) and PSUR activities already in place? What is the intention of the pilot?

The implementation of the risk-prioritized PSUR-RRP fits into a broader PV framework that is being established at Health Canada. The intent of this initiative is to provide a systematic and integrated review approach for the voluntary (i.e. unsolicited) submission of PSURs, including the use of regulatory tools to support and enhance pharmacovigilance review activities during the pre-market review, as well as, the post-authorization of health products.

Information generated from the pilot will be used to determine how PSURs can best integrate with ongoing and future PV activities (e.g. Development Safety Update Reports (DSURs) and Risk Management Plans (RMPs)). Data generated from the pilot will also allow Health Canada to better determine the uptake of resources in PSUR reviews using performance-based metrics.

4. How does the PSUR-RRP relate to other 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 and integrated approach to the regulation of pharmaceuticals and biologics that can be implemented throughout the lifecycle of these products. The PSUR-RRP is an initiative under the Health Products and Food Branch's *Blueprint for Renewal II*, a long-term policy framework for improving the regulatory system for health products and food. PSUR review is intended to be part of the 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. For this reason, the PSUR is recognized as a key component of the lifecycle approach to health product regulation.

5. Does the implementation of a risk-prioritized PSUR-RRP relate to the federal government's Food and Consumer Safety Action Plan?

The *Food and Consumer Safety Action Plan* (Action Plan) is an integrated and risk-based action plan that rests on three key pillars: active prevention, targeted oversight, and rapid response. PSUR review is recognized as a key component of the Action Plan for health products and links to these three key pillars. A PSUR is a useful PV tool used to monitor the worldwide safety profile of a particular marketed product and to identify current or emerging safety concerns. The implementation of the PSUR-RRP improves the regulatory oversight of drug products by

making MAHs more accountable for the ongoing monitoring and reporting of safety issues and will improve earlier detection of potential safety risks. Both PV and risk management planning activities by industry and regular reporting to the regulator will enable rapid responses to identified risks.

6. What products and/or product lines will be included in the PSUR-RRP? How will they be managed?

The PSUR-RRP will only apply to voluntary PSUR submissions received from Market Authorization Holders (MAHs) covering human drugs, specific to the following product lines:

- Pharmaceuticals;
- Biologics and biotechnology products;
- Radiopharmaceuticals; and,
- Vaccines (therapeutic and preventative).

Under the two (2) year PSUR-RRP, voluntary PSUR submissions will undergo risk-prioritized reviews. They will be received, processed, and tracked, using a single window approach using the Drug Submission Tracking System (DSTS) through the Submission and Information Policy Division (SIPD).

7. If the PSUR is not solicited by Health Canada, are MAHs required to submit a PSUR?

Section C.01.016 of Division 1 of the Food and Drug Regulations requires the MAH to analyze adverse drug reaction data for safety concerns and prepare an Annual Summary Report (ASR), and notify the Minister if the

MAH concludes there is a significant change in the benefit-risk profile of their product relating to its safe use. In most cases, PSURs are submitted in lieu of the ASRs.

All voluntary PSUR submissions will be assessed by Health Canada and if specific safety issues emerge for individual products the MAHs may be requested to submit PSURs (i.e. Requested Ad Hoc; Requested Periodic) at established intervals, or until the assessment/monitoring of the safety issue has been resolved, or, a request is made to submit additional safety information.

8. How should PSURs be presented to Health Canada?

A single PSUR may cover all products containing the same active substance(s) licensed by one MAH. The report should include all dosage forms and formulations, as well, as all indications, associated with the active ingredient(s). Within the PSUR, separate presentations of data for different dosage forms, indications or populations (for example, children vs. adults) may be appropriate, however an overview of the combined data should also be provided. The content and format of PSURs should be in accordance with International Conference on Harmonisation Guideline Topic E2C (ICH E2C) and its addendum report.

As per Guidance documents posted on the Health Canada Web site, currently there are two acceptable formats in which MAHs can file electronic PSUR submissions. The two formats are:

- Electronic submission in eCTD format
- Electronic submission in non-eCTD format

PSUR submissions in eCTD format on CD/DVD should be accompanied by a paper cover letter as announced in the Notice *Increased Scope of Submissions being accepted in Electronic Common Technical Document*

(eCTD) Format and acceptance of electronic-only submissions.

If PSUR submissions are not submitted in eCTD format, MAHs are recommended to submit them in electronic format as PDF files in accordance to the February 2008 notice *Release of Health Canada's Revisions to"1.6 Electronic Review Documents" in Draft Guidance for Industry: Preparation of New Drug Submissions in the CTD Format*.

The electronic submission in PDF format is the legal document for PSUR submissions in the "non-eCTD format". The naming convention used for the PDF file is up to the MAH's discretion, however meaningful names should be applied. The CD/DVD including both the electronic copy of the PSUR and the cover letter should be accompanied by a paper cover letter. ***No paper copy of PSUR submissions should be submitted to Health Canada***.

*Note: For preventative vaccines, a single electronic copy is required and it should be submitted to the Submission and Information Policy Division (SIPD). SIPD will forward an electronic copy the Public Health Agency of Canada (PHAC).

9. What is an addendum report? When is it required?

An addendum report is an update to the most recently completed PSUR, when a requested or required report covers data that fall outside the defined period. This may be the case when:

- The requested or required safety update report is outside the usual International Birth Date (IBD) reporting cycle, when synchronizing IBDs.
- A time period greater than 3 months for a 6-monthly or a yearly PSUR, and more than 6 months for a longer-interval PSUR, has elapsed since the data lock point (DLP) of the most recent PSUR.

PSUR addendum reports can be used if the period of PSUR data to be covered falls outside the defined period for PSUR submission.

The addendum report should summarize the safety data received between the DLP of the most recent PSUR and the requested cut-off date. It is not intended to include an in-depth analysis of the additional cases (as these should be included in the next regular PSUR). However in case of a renewal application, the MAH is requested to include an in depth analysis of the cases in the PSUR addendum report as part of the clinical overview.

MAHs must be aware that the next regular PSUR should cover the period since the DLP of the last submitted PSUR and the cases covered by the addendum should be included again.

The format of the addendum should be in line with ICH E2C and its addendum.

10. What is the International Conference on Harmonisation?

The International Conference on Harmonisation (International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use) (ICH) 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 prevent 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);
- the Japanese Pharmaceutical Manufacturers Association (JPMA);
- the United States Food and Drug Administration (FDA); and
- the Pharmaceutical Research and Manufacturers of America (PhRMA).

There are also three ICH observers:

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

In 1996, ICH endorsed the Clinical Safety Data Management Guideline (known as "ICH E2C"), which provides guidance on the format and content of safety updates, which need to be provided at intervals to regulatory authorities after products have been marketed. The guideline is intended to ensure that the worldwide safety experience is provided to authorities at defined times after marketing with maximum efficiency and avoiding duplication of effort. As an observer to ICH, Health Canada has committed to adopt and implement the ICH guidelines.

11. Where do I submit the PSUR?

All PSUR submissions will be processed and tracked using the Drug Submissions Tracking System (DSTS) managed by the Submission and Information Policy Division (SIPD). As of October 31, 2010, MAHs are required to submit PSURs and related information directly to the Office of Submissions and Intellectual Property (OSIP).

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