Health Canada Santé Canada

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Notice

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Adoption of the International Conference on Harmonisation (ICH) Guidance on Periodic Benefit Risk Evaluation Report - ICH Topic E2C(R2), as of March 1, 2013

As an official observer to, and active participant in the International Conference on Harmonisation (ICH), Health Canada is committed to the adoption[1] and implementation of ICH guidances. Health Canada is aware that other regulators have implemented the ICH E2C(R2) guidance and Periodic Benefit Risk Evaluation Report (PBRER) reporting in their country/region. The Department is moving towards implementation in Canada in order to align with international best practices and reduce the burden on industry by allowing them to submit either a Periodic Safety Update Report (PSUR) or a PBRER to satisfy the applicable regulatory requirements in Canada.

Therefore, by way of this Notice, Health Canada is advising stakeholders that, as of March 1, 2013, the Department is adopting the ICH E2C(R2) guidance and will accept either PSURs or PBRERs for review in fulfilment of applicable regulatory requirements. This Notice supersedes the *Notice Regarding the Implementation of a Risk-Prioritized Periodic Safety Update Report Regulatory Review Pilot at Health Canada, including the adoption of International Conference on Harmonisation (ICH) Guidance Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs - ICH Topic E2C* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/vigilance/notice_avis_psur-rrp_pecr-rppv-eng.php).

1. Regulatory Framework for PBRER Review

Section C.01.018[2] of Division 1 of the *Food and Drug Regulations* requires the Market Authorization Holder (MAH) to analyze adverse drug reaction data and prepare an annual summary report. Annual summary reports are to be submitted when requested by Health Canada. In addition, Section C.01.018(4) requires that the MAH notify Health Canada without delay if there has been a significant change in what is known about the risks and benefits of the drug during the period covered by the report.

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1 In adopting this International Conference on Harmonisation guidance, Health Canada endorses the principles and practices described therein and commits to taking the necessary steps to fully implement the guidances in its pharmacovigilance program activities.

2 http://laws.justice.gc.ca/eng/regulations/C.R.C.,_c._870/page-203.html#h-154.

As of the date of this Notice, Health Canada will accept annual summary reports in the PBRER format and content as outlined in the ICH E2C(R2) guidance in fulfillment of the requirements under C.01.018 to prepare annual summary reports. It is the preference of Health Canada that PBRERs be prepared using the International Birth Date[3] (IBD) of the product and the time interval for submission outlined in the ICH E2C(R2) guidance. It should be noted that MAHs are expected to prepare annual summary reports for all their health products with an active Drug Identification Number (DIN), however, they need to submit to Health Canada only upon request.

Under the current regulatory framework for annual summary reporting, Health Canada may request additional information on a case-by-case basis or in follow-up to a PBRER review.

2. Objectives of PBRER Review at Health Canada

Objectives of adoption of ICH E2C(R2) and PBRER review include:

- ongoing evaluation of all new and cumulative information that could have an impact on the benefit-risk profile of the health product;
- supporting the life cycle approach to product vigilance;
- strengthening the link between risk assessment and actions taken to minimize risk;
- aligning product vigilance with international best practices; and,
- reducing the burden on industry that would result if MAHs were to have to produce PSURs for Health Canada and PBRERs for other jurisdictions.

3. Scope of Products Covered by PBRERs

The scope of products covered by PBRERs includes:

- pharmaceuticals;
- biologics;
- biotechnology products;
- radiopharmaceuticals;
- preventative vaccines; and,
- therapeutic vaccines.

4. Transition to PBRER Reporting

As of March 1, 2013, MAHs may submit annual summary reports in the PBRER format when requested to do so by Health Canada. Health Canada will also continue to accept annual summary reports in the PSUR format as outlined in Section 5 of the *Guidance Document for Industry - Reporting Adverse Reactions to Marketed Health Products*. All applicable Health Canada guidance documents related to PSUR will be updated in the future to reflect the current requirements and approach.

Please follow the procedures outlined in this Notice until such a time as otherwise notified.

[3] The date of the first marketing authorisation for any product containing the active substance granted to any company in any country in the world.

5. Notification to Health Canada of a Significant Change in What is Known About the Risks and Benefits of a Health Product

In accordance with the Food and Drug Regulations, in preparing the annual summary report, if the MAH concludes that there has been a significant change in what is known about the risks and benefits of the health product, the MAH must notify Health Canada in writing without delay (see Health Canada contact information provided in Appendix A.4). Potential reasons for notification include, but are not limited to, a significant change in the frequency or severity of a known risk or the identification of a previously unknown risk.

The notification should include a cover letter indicating that the information is being sent pursuant to the notification requirements detailed in C.01.018(4) and a copy of the most recent completed annual summary report, which may be provided in either PSUR or PBRER format.

6. PSUR/PBRER Covering Letter

All PSURs/PBRERs should be accompanied by both an electronic and a paper cover letter (see Appendix A). The cover letter should indicate the submission type [for example (e.g.) PSUR or PBRER] as well as the reason for the submission (e.g. significant change in what is known about the risks and benefits of the health product, requested PSUR-c/PBRER-c, requested periodic, requested ad hoc or voluntary submitted PSUR/PBRER). All PSURs/PBRERs should also be accompanied by an electronic Annual Summary Report Checklist (see Appendix A.2 and A.3).

Please refer to the Appendices below for instructions on submitting PSURs or PBRERs to Health Canada:

Appendix A. Instructions for Submitting Periodic Safety Update Reports (PSURs) and Periodic Benefit Risk Evaluation Reports (PBRERs) in Electronic Format

Appendix B. Annual Summary Report Checklist (including PSUR or PBRER format)

Appendix A: Instructions for Submitting Periodic Safety Update Reports (PSURs) and Periodic Benefit Risk Evaluation Reports (PBRERs) in Electronic Format

A.1 General Requirements

PSURs/PBRERs should be submitted to Health Canada electronically on CD/DVD; **No paper copy of the PSUR/PBRER should be submitted**. Electronic documents will be uploaded onto the Health Canada viewing tool, where they will be immediately accessible to Health Canada staff involved with the review of the regulatory activity/submission. This will contribute to good record management and ensure authenticity, integrity, availability, traceability, and non-repudiation of the data.

All PSURs/PBRERs should be submitted with an electronic **and** a paper cover letter which indicates the submission type (PSUR/PBRER/PSUR-C/PBRER-C) as well as the reason for the submission;

- significant change in what is known about the risks and benefits of the health product;
- VOLUNTARY PSUR/PBRER - unsolicited information;
- REQUESTED PERIODIC PSUR/PBRER - requested by Health Canada (for example Risk Management Plan (RMP) follow-up or post-authorization commitment);
- REQUESTED AD HOC PSUR/PBRER - submitted as a one-time request made by either the pre-market review directorate reviewing the associated regulatory activity/submission or by MHPD (the requestor should be specified in the cover letter).

All PSURs/PBRERs should also be accompanied by an electronic Annual Summary Report Checklist (see Appendix A.2 and A.3).

Note: a **PSUR-C/PBRER-C** is submitted to support the fulfillment of a Notice of Compliance with Conditions (NOC/c).

Health Canada encourages MAHs to submit the PSUR/PBRER documents as PDF (1.4 to 1.7) files. PDF versions of documents should be generated from electronic source documents and not from scanned material, except where access to the source electronic file is unavailable or where a signature is required. It is important that PDF files be properly bookmarked. The following are recommended as good bookmarking practices:

- Documents of ten pages or more should be bookmarked.
- Bookmarks are equivalent to and should be organized similar to a document table of contents, and should not include the regulatory activity/submission level.
- Sections, subsections, tables, figures, and appendices should all be bookmarked.
- Too many levels of bookmarks are inefficient; in most instances, four levels of bookmarks should be sufficient:

1 Heading
  1.1 Subheading
    1.1.1 Sub-subheading

1.1.1.1 Sub-Sub-Subheading

Health Canada recognizes that bookmarks are generated automatically from document headings, but nevertheless recommends they be kept concise.

A.1.1 Folder Structure and Folder Content

The content of the electronic media should be organized in folders. **Files submitted electronically should neither be zipped nor password protected.**

- With the exception of the file extension, the file naming convention within each folder is left to the MAH. However, Health Canada suggests that the file names be kept as brief and meaningful as possible.
- ICH requires that the file names be limited to a maximum of 64 characters, including the file extension. See the ICH *Electronic Common Technical Document Specification* (Version 3.2), "Name," pages 2-5.

A.1.2 Media for Submitting Electronic Data

The media formats acceptable when submitting any electronic regulatory activity/submission are:

- Compact Disc-Recordable (CD-R) conforming to the Joliet specification;
- Digital Versatile Disc-Random Access Memory (DVD-RAM) Universal Disc Format (UDF) standard;
- Digital Versatile Disc-Recordable (DVD+R/-R) recorded in the Universal Disc Format (UDF) standard;
- Universal Serial Bus Version 2.0 [Universal Serial Bus (USB) 2.0] drive;

These are the formats that are currently supported. Contact Office of Submissions and Intellectual Property (OSIP) for other formats that may be acceptable at the time of filing. See below for full contact information.

Media should not be password protected.

MAHs should provide all documents on a single disc/drive. Duplicate copies are not required. All media should be labelled. The labels on the disc/drive should contain the following information:

- MAH name and brand name;
- eCTD Identifier *(if applicable)*;
- Sequence number *(if applicable)*;

- "Protected B"[4];
- Virus-free certification, the software used for the virus check, and the date of the virus definition file or files; and
- Month and year of filing.

Subsequent to burning the CD or DVD or transferring data to a USB, MAHs should ensure that **all** files can be opened and that no files are corrupt.

As per guidance documents posted on the Health Canada Web site, there are currently two acceptable formats in which MAHs can file PSUR/PBRER regulatory activities/submissions.

- Electronically in eCTD format;
- Electronically in non-eCTD format.

A.2 eCTD Format Requirements

The PSURs/PBRERs are eligible for filing in the eCTD format. The Annual Summary Report Checklist (Appendix B) should be filed as a leaf element under the *m1-2-3-certification-and-attestation-forms* heading and the PBRER should be filed as a leaf element under the *m-5-3-6-Reports of Postmarketing Experience* heading. The naming convention used for the leaf titles is up to the MAH's discretion; however, meaningful names should be applied.

When compiling regulatory activity in eCTD format using the Canadian Module 1 schema v2.2, sponsor should use "PSUR-PV" as the Regulatory Activity Type.

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.

A.3 Non-eCTD Format Requirements

If PSURs/PBRERs are not submitted in eCTD format, MAHs should submit them in electronic non-eCTD format. The Annual Summary Report Checklist should be filed in the section "1.2.3 Certification and Attestation Forms and the PBRER should be filed in the section "5.3.6 Reports of Postmarketing Experience" 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.*

[4] "Protected" status identifies information the unauthorized disclosure of which could reasonably be expected to cause injury to private interests. "Protected B" indicates a medium degree of potential injury. See *Government Security Policy* (July 2009), Section 10.6, "Identification of Assets." The policy is available at < http://www.tbs-sct.gc.ca/pol/doc-eng.aspx?id=12322>.

A.4 Contact Information

As of March 1, 2013 MAHs are required to submit PSURs/PBRERs and related information directly to OSIP using the following address:

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 inquiries related to electronic format, please contact Health Canada using the following e-mail address:

E-mail: ereview@hc-sc.gc.ca

If you have any questions or comments about the above messaging, please do not hesitate to contact Marketed Health Products Directorate (MHPD) for clarification. All enquiries pertaining to this Notice should include the phrase: "PBRER Notice- ORMS", in the subject line.

Email: mhpd_dpsc@hc-sc.gc.ca

Appendix B:

Annual Summary Report Checklist (including PSUR and PBRER)

C.01.018.

(1) The manufacturer shall prepare an annual summary report of all information relating to adverse drug reactions and serious adverse drug reactions to the drug that it received or became aware of during the previous 12 months.

(2) The annual summary report shall contain a concise, critical analysis of the adverse drug reactions and serious adverse drug reactions to the drug.

(3) In preparing the annual summary report, the manufacturer shall determine, on the basis of the analysis referred to in subsection (2), whether there has been a significant change in what is known about the risks and benefits of the drug during the period covered by the report and shall include its conclusions in this regard in the summary report.

(4) If, in preparing the annual summary report, the manufacturer concludes that there has been a significant change, it shall notify the Minister without delay, in writing, unless this has already been done.

(5) The Minister may, for the purposes of assessing the safety and effectiveness of the drug, request in writing that the manufacturer submit to the Minister one or both of the following:

(*a*) the annual summary reports;

(*b*) the case reports relating to the adverse drug reactions and serious adverse drug reactions to the drug that are known to the manufacturer.

(6) The Minister shall, after giving the manufacturer an opportunity to be heard, specify a period for the submission of the annual summary reports or case reports, or both, that is reasonable in the circumstances, and the manufacturer shall submit the reports within that period.