Health Canada Santé Canada

Our Mandate:
To promote good nutrition and informed use of drugs, food, medical devices and natural health products, and to maximize the safety and efficacy of drugs, food, natural health products, medical devices, biologics and related biotechnology products in the Canadian marketplace and health system.

Inspectorate Program

Guidance Document

Post-Market Reporting Compliance (PMRC) Guidelines

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Disclaimer
This document does not constitute part of the Food and Drugs Act (Act) or its associated regulations and in the event of any inconsistency or conflict between that Act or Regulations and this document, the Act or the Regulations take precedence. This document is an administrative document that is intended to facilitate compliance by the regulated party with the Act, the Regulations and the applicable administrative policies. This document is not intended to provide legal advice regarding the interpretation of the Act or Regulations. If a regulated party has questions about their legal obligations or responsibilities under the Act or Regulations, they should seek the advice of legal counsel.

Canada

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1.0 Introduction

The *Food and Drug Regulations*, more specifically sections C.01.016, C.01.017, C.01.018, C.01.019, C.01.020, C.08.007 and C.08.008, set forth regulatory requirements for manufacturers, including but not limited to, the reporting of adverse drug reactions (ADR) and the reporting of unusual failures in efficacy of new drugs to Health Canada. As part of Health Canada's mandate to maximize the safety, quality and efficacy of health products, Health Canada implemented on August 1, 2004, an inspection programme for Post-Market Reporting Compliance (PMRC). The PMRC inspection programme is intended to ensure that manufacturers are in compliance with the regulatory requirements for the receipt, analysis and submission of drug safety information to Health Canada, including the reporting of domestic and foreign adverse drug reactions within 15 days, the preparation of annual summary reports, the maintenance of records related to reports and case reports and unusual failure in efficacy, and the reporting of domestic cases of unusual failures in efficacy for new drugs within 15 days. Within the context of the PMRC inspection programme, MAH and importers are considered manufacturers as their name appears on the label and as such, are subject to PMRC inspections.

These guidelines on PMRC pertain to Division 1 (C.01.016 to C.01.020) and Division 8 (C.08.007(h) and C.08.008(c)), of Part C of the *Food and Drug Regulations*. The guidelines were developed by Health Canada and are designed to facilitate compliance by the regulated industry and to enhance consistency in the application of the regulatory requirements.

The content of this document should not be regarded as the only interpretation of the *Food and Drug Regulations*, nor does it intend to cover every conceivable case. Alternative means of complying with the *Food and Drug Regulations* can be considered with the appropriate justification.

2.0 Purpose

The purpose of this guidance document is to provide interpretive guidance for Part C, Division 1 (C.01.016 to C.01.020) and Division 8 (C.08.007(h) and C.08.008(c)) of the *Food and Drug Regulations*. These guidelines are designed to facilitate compliance by the regulated industry and to enhance consistency in the application of the regulatory requirements.

3.0 Scope

The *Food and Drug Regulations* set forth regulatory requirements for manufacturers to report adverse drug reactions and to report unusual failure in efficacy of new drugs to Health Canada. This guide covers the following marketed drugs in Canada for human use which are subject to the above requirements of the *Food and Drug Regulations*:

- -pharmaceuticals,
- -biologics, including blood products and therapeutic and diagnostic vaccines,
- -preventative vaccines (including immunization schedule vaccines, flu vaccines, and vaccines for travel),
- -medical gases, and
- -radiopharmaceuticals.

This guide does not currently apply to:

- -hard surface disinfectants,

-veterinary products,
-natural health products, and
-whole blood and blood components.

Within the context of the PMRC inspection programme, MAH and importers are considered manufacturers as their name appears on the label and as such, are subject to PMRC inspections.

4.0 Regulation

Please note that an interpretation may apply to more than one regulation and in those instances, the interpretation is only stated once.

Prohibition - C.01.016

No manufacturer shall sell a drug unless the manufacturer complies with the conditions set out in sections C.01.017 to C.01.019.

Serious Adverse Drug Reaction Reporting - C.01.017

Regulation

The manufacturer shall submit to the Minister a report of all information relating to the following serious adverse drug reactions within 15 days after receiving or becoming aware of the information, whichever occurs first:

(*a*) any serious adverse drug reaction that has occurred in Canada with respect to the drug; and

(*b*) any serious unexpected adverse drug reaction that has occurred outside Canada with respect to the drug.

Rationale

Market Authorisation Holders (MAH) and importers should have a robust system in place that ensures that adequate pharmacovigilance information is provided to Health Canada within the prescribed timelines and with quality data. The ultimate objective of the process is thereby managing the risks and benefits of health products to Canadians.

Interpretation

Note: Importers who have been delegated the activities related to pharmacovigilance by the foreign MAH are also required to meet the requirements in this section. All importers should have available evidence that the below requirements were met.

Adverse Reaction Reporting

1.0 Procedures and processes

1.1 MAHs and importers should have in place systems and procedures for the receipt, handling, evaluation and reporting of ADRs that are adequate to effectively sustain ADR reporting within 15 days of receipt to Health Canada of domestic serious unexpected ADRs, foreign

serious unexpected ADRs, and domestic serious expected ADRs, as well as any follow-up information for initial case reports. This includes, but is not limited to, all foreign serious unexpected ADR reports involving the MAH's foreign products with the same combination of active ingredients that is also marketed in Canada irrespective of variations in the formulation, dosage form, strength, route of administration, or indication. These must be reported to the MHPD in accordance with the *Food and Drug Regulations* (e.g., a MAH that sells a marketed health product in Canada with active ingredients X, Y, and Z, must report all foreign serious unexpected ADR reports involving their foreign products with active ingredients X, Y, Z).

1.2 MAHs should have in place adequate procedures for adverse drug reaction receipt, handling, evaluation and reporting and should include at the minimum the following:

1.2.1 Requirement to report within 15 calendar days of receipt by the manufacturer, reports of serious adverse drug reactions occurring within Canada, and serious unexpected adverse drug reactions occurring outside of Canada and any unusual failure in efficacy for new drugs;

1.2.2 Address all the specific Canadian regulatory requirements, such as when notification is required, definition of serious and non-serious reactions, retention of all records associated with adverse drug reaction, etc.

1.2.3 Requirement to have a health care professional to evaluate and assess adverse drug reaction reports, including the process to review ADRs;

1.2.4 Identifying the minimum criteria for submitting a case

1.2.5 Identifying key personnel who are responsible for forwarding the adverse drug reactions reports to Health Canada;

1.2.6 Procedure on how adverse drug reactions are tracked/logged in;

1.2.7 Procedure on how the firm is to be notified of foreign serious unexpected drug reactions;

1.2.8 Requirements and concise methodology to accurately assess an adverse drug reaction report, which includes, but is not limited to: Patient Information, Description of ADR, Drug Product(s) involved, etc.

1.2.9 The responsibilities for the final approval of complaint/adverse drug reaction evaluation and appropriate follow-up;

1.2.10 Reference to the contact information for the appropriate department/branch/directorate within Health Canada where reports are to be submitted;

1.2.11 Requirement to effectively follow-up with case reports, to document all attempts to obtain follow-up information and submit information to the appropriate department/branch/directorate within Health Canada as it becomes available;

1.2.12 Requirement to conduct a critical analysis of adverse drug reaction reports received and prepare a summary report on an annual basis, or at the request of Health Canada;

1.2.13 Requirement to effectively maintain records of adverse drug reactions for 25 years after the day on which they were created;

1.3 Importers should have in place adequate procedures for adverse drug reaction receipt, handling, evaluation (i.e., if complaints or ADR) and reporting to the MAH and should include at the minimum the following:

1.3.1 Procedure on how complaints and adverse drug reactions are tracked/logged in;

1.3.2 Procedure on how complaints are assessed in order to determine if it is an ADR;

1.3.3 Identifying key personnel who are responsible for forwarding the adverse drug reactions reports to the MAH;

1.3.4 Requirement to report immediately ADRs to the MAH;

1.3.5 Requirement to follow up with the MAH to ensure that ADRs have been assessed and sent to Health Canada, if required;

1.3.6 Requirement to maintain records of all ADRs received and ADRs sent to the MAHs and subsequent correspondence; and

1.3.7 Requirement to effectively maintain records of adverse drug reactions for 25 years after the day on which they were created.

1.4 Procedures are written and reviewed by adequately trained personnel and approved by personnel who have appropriate authority

1.5 Procedures are immediately made available to all relevant personnel involved in pharmacovigilance activities when the procedures are effective.

1.6 Procedures are reviewed on a periodic basis to ensure that they accurately reflect current practice.

1.7 Significant deviations from procedures relating to pharmacovigilance activities should be documented.

1.8 When part or all pharmacovigilance activities are performed by a third party, MAH and importers should review procedures defined above in Interpretation 1.2 and 1.3 respectively to ensure that procedures are adequate and compliant with applicable requirements stated in the *Food and Drug Regulations* and all requirements outlined in the documents indicated in the Associated Documents sections. Copies of the procedures should be retained by MAH.

2. Receipt/Collection and Collation of ADR Data

2.1 Market Authorisation Holder and Importers

2.1.1 All suspected adverse drug reactions are recorded, tracked and logged appropriately and transferred to the personnel undertaking pharmacovigilance activities.

2.1.2 Mechanism should be in place to ensure that all ADRs have been appropriately identified and transferred to the relevant department.

2.1.3 Adequate records of all pharmacovigilance data received should be maintained.

2.1.4 An unique identifier is assigned to each suspected ADR received.

2.1.5 Periodic checks of information, including correspondence files, line listings or database reviews is done by the MAH and importers to ensure that all pharmacoviligance data from technical complaints and medical information enquiries have been appropriately recorded and classified, for example serious ADR, in the pharmacoviligance system. The MAH and importers should define the periodicity of these checks.

3. Evaluation of ADR data

3.1 Market Authorisation Holder

3.1.1 ADR reports are appropriately coded. The Medical Dictionary for Regulatory Activities (MedDRA) terminology is recommended to code ADR reports.

3.1.2 The evaluation, including but not limited to, seriousness and expectedness assessment is completed in a timely manner for every ADR.

3.1.3 Processes are in place to validate the information provided in a case, if applicable.

3.1.4 The decision-making process to determine if a case is reportable is appropriately documented. When a case is found not reportable, justification is provided and documented.

3.1.5 Process about the causality of solicited reports should be documented in procedures, including that qualified personnel should be assessing these and rationale for determining reportability should be documented

3.1.6 Reports of similar ADRs from 2 or more sources

3.1.6.1 A mechanism should be in place to identify pharmacovigilance data that were reported to the MAH more than once.

3.1.6.2 When similar reports are found, a root cause analysis should be performed and corrective actions taken, if appropriate. Documentation relevant to that analysis should be kept on file.

3.1.6.3 Multiples ADR reports of the same adverse drug reactions can be deleted within the pharmacovigilance system and a copy of the record is maintained allowing for auditing of the record in the future.

3.1.6.4 Documented procedure should be in place describing when ADR reports may be logically deleted and the process to do so.

3.1.6.5 Record of why a case has been deleted should be retained.

3.1.7 Change in the assessment of ADRs

3.1.7.1 Upon receipt of additional follow-up information, ADR reports should be re-evaluated.

3.1.7.2 All ADR reports that have been upgraded to serious are to be sent to Health Canada within the prescribed timelines.

3.1.7.3 MAH should notify Health Canada when a ADR report that was submitted to Health Canada has been downgraded to non-serious.

3.1.7.4 Rationale for upgrading or downgrading an ADR report should be documented.

4. Reporting of ADR data

4.1 Market Authorisation Holder

4.1.1 All ADRs that meet the requirements of the *Food and Drug Regulations* must be reported to the MHPD in accordance with the *Food and Drug Regulations*.

4.1.2 Periodic checks are performed to ensure that the appropriate ADR reports are sent to Health Canada.

4.1.3 Periodic checks are performed to ensure that the appropriate data is entered in the system, safety database.

4.2 Importers

4.2.1 All suspected ADRs received are sent to the MAH, and should therefore be reported to MHPD by the MAH.

5. Literature Search

5.1 Market Authorisation Holder

5.1.1 Procedure should be in place describing the process to perform literature searches, including but not limited to how the search is done, the database used, and the periodicity of those searches.

5.1.2 Searches, on the drug and active pharmaceutical ingredients, in published literature are performed on a regular basis.

5.1.3 ADRs found during literature searches are classified according to their seriousness and expectedness. These assessments are retained and well documented.

5.1.4 ADR reports from the scientific and medical literature must be reported to the MHPD in accordance with the Food and Drug Regulations. For additional information, refer to MHPD's document entitled "Guidance Document for Industry - Reporting Adverse Reactions to Marketed Health Products"

5.1.5 Results of the literature searches are documented.

5.1.6 When literature search is perform by a third party, contractual agreements describing each party responsible should exist.

6. Self-inspection program

6.1 A self-inspection program that covers all departments that may receive ADR reports or that are involved in pharmacovigilance activities may help to ensure compliance with the appropriate sections of the *Food and Drug Regulations* applicable to adverse drug reaction reporting. Self-inspection programs should be in place and should include;

6.1.1 A comprehensive written procedure that describes the functions of the self-inspection program

6.1.2 Periodic self-inspections that are carried out at defined frequencies, which are documented.

6.1.3 Reports on the findings of the self-inspections and on corrective actions. These reports should be reviewed by appropriate senior company management. Corrective actions should be implemented in a timely manner.

6.2 Self-inspections that are conducted by personnel independent from the pharmacovigilance department are suitably qualified to perform and evaluate the inspections.

Personnel and Training

7. Market Authorisation Holder and Importers

7.1 The individual in charge of the pharmacovigilance department:

7.1.1 is a qualified healthcare professional with pertinent training, and expertise to conduct pharmacovigilance duties;

7.1.2 Delegates duties to a qualified healthcare professional with pertinent training and expertise to conduct pharmacovigilance duties.

7.2 The Qualified healthcare professional;

7.2.1 has knowledge of all applicable sections of the *Food and Drug Regulations* related to the adverse drug reaction reporting requirements, and of key pharmacovigilance activities performed as part of the MAH's pharmacovigilance system.

7.2.2 is responsible for establishing and managing/maintaining a system which ensures that information concerning all suspected adverse drug reactions that are reported to the personnel of the company and to medical representatives is collected and evaluated.

7.3 All responsible personnel have their specific duties recorded in a written description and have adequate authority to carry out their responsibilities. All personnel are aware of the principles of pharmacovigilance that affect them, and all personnel receive relevant initial and continuing training and are periodically assessed against their job responsibilities.

7.4 When key personnel, including but not limited to customer service, sale representatives and receptionist, are absent, qualified personnel are appointed to carry out their duties and functions.

7.5 A person with adequate experience and education, as defined in Int 7.1 and 7.2, evaluates information in respect of a potential AR, assesses the seriousness, expectedness, and reportability of ADRs, and determines if the ADR report qualifies for expedited reporting (within 15 days) or if the report is to be included in the annual summary.

7.6 Training is provided prior to implementation of new or revised SOPs. Records of training are maintained.

7.7 Consultants and contractors have the necessary qualifications, training, and experience, as defined in Int 7.1 and 7.2, to advise on the subjects for which they are retained. In cases where consultants and/or contractors are employed, contractual agreements as detailed in Int. 8 should be in place. In addition, the MAH and importers or person(s) appointed by the MAH and importers should assess the consultants' and/or contractors' qualifications and knowledge of the regulatory requirements pertaining to adverse drug reaction reporting.

Contractual Agreements

8. Market Authorisation Holder and Importer

8.1 Contractual agreement should exist with every party, including third-party private label or other companies whose name is included in the product information or appears on the label, who conducts pharmacovigilance activities and should include;.

8.1.1 who is responsible for the critical analysis of the summary reports, and what methodology is utilized to conduct the critical analysis,

8.1.2 who is responsible to report ADR,

8.1.3 who is responsible for conducting literature searches,

8.1.4 processes by which an exchange of safety information, including timelines and regulatory reporting responsibilities, are taking place between the manufacturer and its partners (including, but not limited to, consultants and contractors).

8.1.5 to notify other party if changes to procedures are made, and

8.1.6 timeframes for exchange of information.

8.2 In the case of foreign manufacturers, the contractual agreement should specify to send foreign serious and unexpected ADR case reports to the MAH in a timely manner so as to promote compliance with regulatory reporting obligations.

8.3 In the case where the importer is responsible for the pharmacovigilance activities, the contractual agreement should specify that the foreign MAH is to send the ADR data in a timely manner.

8.4 All records (including, but not limited to, contracts and safety data/ADR data) are available on the premises of the MAH and the importer.

8.5 When there is a transfer of market authorization/mergers, contractual agreement should exist between the previous manufacturer and the new one outlining each party responsibility.

8.6 Contractual agreement is shared and signed off by each party.

8.7 Contractual agreement are to be reviewed periodically in order to reflect current regulations and practices.

Validation of Computerized Systems

9. Market Authorisation Holder, Importer, and all parties involved in pharmacovigilance activities who use an electronic system

9.1 Data of the validation of system(s) used for recording, evaluating, and tracking complaints and ADRs should be available.

9.2 Computerized systems are validated, and spreadsheets to track ADRs are qualified and system are periodically and suitably backed up at predefined intervals.

9.3 Validation is periodically reviewed at predefined intervals to assess the current suitability of systems and past and proposed changes.

Product Complaints

10. Market Authorisation Holder and Importers

10.1 Written procedures should be in place describing the handling of all complaints regarding a drug product.

10.2 The procedure should include:

10.2.1 provisions for timely and thorough review to determine whether the complaint represents an AR;

10.2.2 clear identification of personnel who receives the incoming correspondence (phone calls, letter, email, etc) relating to potential ADRs through product complaints;

10.2.3 how report control numbers assigned as defined in Int. 2.1.4; and

10.2.4 clear and defined processes on ADR/complaint investigation, evaluation and follow-up.

10.3 System should be in place to register all calls received by the consumer service ensuring traceability.

Annual Summary Report and Case Reports - C.01.018

Regulation

(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 it knows 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 submits 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.

Rationale

The annual summary report is a practical and achievable mechanism for summarizing interval safety data, and for conducting an overall safety evaluation. It is a tool for MAHs to conduct systematic analyses of safety data on a regular basis. One of the objectives of the annual summary report is to find emerging and/or urgent safety issues.

Interpretation

Note: The MAH is responsible for this section of the *Food and Drug Regulations*. Importers who have been delegated that responsibility by the foreign MAH are also required to meet the requirements in this section. All importers should have available evidence that the below requirements were met.

1. Written procedure for the preparation of the annual summary report (ASR) which includes, but is not limited to:

    1.1 A requirement to submit the ASR upon request to Health Canada within the time frame specified by the Minister when the report is requested

    1.2 The sections that should be included in the summary report as defined in Section 5.1 of MHPD's guidance document entitled *Guidance Document for Industry - Reporting Adverse Reactions to Marketed Health Products*

    1.3 List of pertinent cases that are to be included in the summary report.

    1.3 A requirement to prepare a summary report on an annual basis for each drug.

    1.4 Documentation on what "annual" dates are used for preparing the ASR.

2. The MAH prepares an ASR 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. This report should include foreign and domestic adverse drug reactions. It should also include expected and unexpected adverse drug reactions as well as all adverse drug reactions related to unusual failure in efficacy of a new drug.

3. The ASR contains a concise, critical analysis of the adverse drug reactions and serious adverse drug reactions to the drug and recommended actions.

4. In preparing the annual summary report, the MAH shall determine, on the basis of the analysis, whether there has been a significant change in what is known about the risks and benefits of the drug since the last annual summary report, and shall include its conclusions in this regard in the summary report.

5. If the MAH advises MHPD when it concludes from the ASR that there is a significant change in what is known about the risks and benefits of a product relating to its safe use, information (including notification of this information to MHPD, without delay) is available on file. The MAH must notify the Minister without delay, in writing, if in preparing the annual summary report the MAH concludes that there has been a significant change.

6. For the purposes of assessing the safety and effectiveness of the drug, the Minister may request in writing that the MAH submit in the time period specified by the Minister:

(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 MAH .

6.1 Requests for information from Health Canada are maintained.

7. If the MAH chooses to use a third party to prepare the ASR, contracts must be in place defining their respective responsibilities.

8. Annual summary report reviewed by Health Canada and for which comments were received by the MAH should be documented and changes implemented in subsequent summary report.

9. Verifications should be performed to ensure the accuracy and completeness of data/ information in the summary report. There checks should be documented.

10. Signal detection

10.1 Written procedure should be in place that adequately describes the way in which the MAH perform signal detection.

10.2 Roles and responsibilities of each person involved in the signal detection process are clearly identified and documented.

10.3 The source of the information to include in the analysis and the method used for signal detection should be documented.

10.4 Actions taken based on the outcome generated from the signal detection activities should be documented adequately and include but not limited to the outcome, decision and actions.

10.5 Data regarding the potential significant change in the risks and benefits of the drugs should be sent to Health Canada and should be documented.

11. Product Monograph (PM), label and leaflet

11.1 The person who assesses ADR has access to the latest approved label and product monograph

11.2 Product information is kept up to date.

11.3 One copy of previous PMs, leaflets and labels are available on file.

11.4 Records are maintained of requests received from Health Canada to update product information documents, if applicable.

11.5 Once a new safety issue has been identified and drug product information is to be updated, procedures should be in place to facilitate timely submission of changes to ensure there is no undue delay in updating documents.

12. Risk Management Plan (RMP)

Note: RMPs are not mandatory, however they may be required as part of a Notice of Compliance with condition. During PMRC inspections, inspectors will verify that these commitments are met.

12.1 RMP should be prepared in accordance with the Notice of compliance with conditions and include at the minimum the following:

12.1.1 what will be done to monitor, including completed studies, on-going studies and progress, any identified or potential risk and how more information will be gathered (pharmacovigilance plan)

12.1.2 a description of the measures that will be required to minimise the risk for each identified and potential risk mentioned in the safety specification (risk minimisation)

12.1.3 it should be product-specific

12.1.4 a plan to monitor the success of risk-minimisation activities and expectations on acceptance criteria for success should be in place

Issue-related Summary Report - C.01.019

Regulations

C.01.019

(1) 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 an issue-related summary report.

(2) An issue-related summary report shall contain a concise, critical analysis of the adverse drug reactions and serious adverse drug reactions to the drug and case reports of all or specified adverse drug reactions and serious adverse drug reactions to the drug that are known to the manufacturer in respect of the issue that the Minister directs the manufacturer to analyze in the report.

(3) The Minister shall, after giving the manufacturer an opportunity to be heard, specify a period for the submission of the report that is reasonable in the circumstances. The Minister may specify a period that is shorter than 30 days if the Minister needs the information in the report to determine whether the drug poses a serious and imminent risk to human health.

(4) The manufacturer shall submit the report within the specified period.

Rationale

The issue-related summary report is a practical and achievable mechanism for summarizing a specific issue with a drug. That summary report contains information such as adverse drug reactions and serious adverse drug reactions to the drug and case reports of all or specified adverse drug reactions and serious adverse

drug reactions to the drug that are known to the manufacturer. It is a tool for Minister to assess the safety and effectiveness of the drug.

Interpretation

Note: The MAH is responsible for this section of the *Food and Drug Regulations*. Importers who have been delegated that responsibility by the foreign MAH are also required to meet the requirements in this section. All importers should have available evidence that the below requirements were met.

1. Written procedure for the preparation of an issue-related summary report upon request from the Minister which includes but is not limited to:

    1.1 A concise, critical analysis of the adverse drug reactions and serious adverse drug reactions to the drug and case reports of all or specified adverse drug reactions and serious adverse drug reactions to the drug that are known to the MAH in respect of the issue that the Minister directs the MAH to analyse in the report.

    1.2 The maintenance of the issue-related summary report prepared by the MAH .

2. A process should be established for the accurate and timely retrieval and output of stored data or records from the pharmacovigilance system.

Maintenance of Records - C.01.020

Regulation

(1) The manufacturer shall maintain records of the reports and case reports referred to in sections C.01.017 to C.01.019.

(2) The manufacturer shall retain the records for 25 years after the day on which they were created.

Rationale

Good documentation is an essential part of the quality assurance system and should therefore be related to all aspects of pharmacovigilance. Its aims are to ensure that the pharmacovigilance department has all the information necessary regarding the safety of a drug and to provide an audit trail that will permit investigation of the history of any drugs that is suspected to be unsafe.

Interpretation

Note: Importers who have been delegated the activities related to pharmacovigilance by the foreign MAH are also required to meet the requirements in this section. All importers should have available evidence that the below requirements were met.

All relevant pharmacovigilance documents (such as associated records of actions taken or conclusions reached) and standard operational procedures (SOP) are prepared by the relevant department. No changes are made without the approval of the qualified person in charge of the pharmacovigilance. Any alteration

made to a document is signed and dated; the alteration permits the reading of the original information. Where appropriate, the reason for the change is recorded.

Any documentation requested for evaluation by Health Canada is provided in one of the official languages.

1. Market Authorisation Holder and Importers

   1.1 Records of serious ADR and annual summary reports maintained by MAH are accessible within 72 hours from the MAH

   1.2. Records are retained for a minimum of 25 years after the day on which they were created.

   1.3 A procedure describes how ADR records are maintained, i.e., name of the filing system or electronic database which would facilitate the management of any such records in a reliable manner that allows for consistent retrieval.

   1.4 Complete records, such as documentation of decisions, documentation of follow-up and follow-up attempts and annual summary reports, are available in ADR files.

   1.5 All computer systems should have in place a security system that prevents unauthorized access and changes to the data.

   1.6. A list of individuals who are authorised to access the system and make data changes should be maintained.

2. The MAH retained all ADR records.

3. The importer retains at the minimum the following documents (depending on their responsibilities) :

   3.1 Evidence that ADRs were sent to Health Canada

   3.2 Evidence that summary reports were prepared on an annual basis, including date of issuance, summary and conclusions.

New Drugs – C.08.007 (h) and C.08.008 (c)

Regulation

C.08.007 (h)

Where a manufacturer has received a notice of compliance issued in respect of a new drug submission or abbreviated new drug submission or a supplement to either submission, the manufacturer shall establish and maintain records, in a manner that enables an audit to be made, respecting...
(*h*) any unusual failure in efficacy of that new drug.

C.08.008 (c)

No manufacturer shall sell a new drug unless the manufacturer has, with respect to all the manufacturer's previous sales of that new drug, furnished to the Minister...
(*c*) within 15 days after the receipt by the manufacturer of information referred to in paragraphs C.08.007(*g*) and (*h*), a report on the information received.

Rationale

The safety and effectiveness of a new drug have not been established, therefore MAH and importers should have a system in place that would allow them to provide to Health Canada, within prescribed time lines, the information related to any unusual failure in efficacy of a new drug product. The underlying principle is that if a product fails to produce the expected intended effect, there may be an adverse outcome for the patient including an exacerbation of the condition for which the health product is being used. The ultimate objective of all endeavours is the product safety.

Good documentation is an essential part of the quality assurance system and should therefore be related to all aspects of pharmacovigilance. Its aims are to ensure that the pharmacovigilance department has all the information necessary regarding the safety of a drug and to provide an audit trail that will permit investigation of the history of any drugs that is suspected to be unsafe.

Interpretation

Note: The MAH is responsible for this section of the *Food and Drug Regulations*. Importers who have been delegated that responsibility by the foreign MAH are also required to meet the requirements in this section. All importers should have available evidence that the below requirements were met.

1. The MAH has systems and procedures in place to receive, evaluate and report to Health Canada within 15 days of the receipt of the information, any unusual failure in efficacy report of new drugs marketed in Canada.

2. The MAH has identified products with new drug status. A new drug is a drug which received a NOC (Notice of Compliance).

3. Criteria defining what is considered an unusual failure in efficacy of a new drug are established by the MAH.

4. Every ADR report related to unusual failure in efficacy that meets the established criteria for reporting unusual failure in efficacy is submitted to Health Canada within the appropriate timeframe (i.e., within 15 days).

5. Qualified personnel (i.e., a qualified health care professional evaluates potential cases of unusual failure in efficacy to determine if the case qualifies for expedited (15-day) reporting. These evaluations and assessments are adequately documented.

6. The complete documentation of ADR reports of unusual failure in efficacy is available for auditing purposes at the MAH premises or is easily accessible within 72 hours.

7. The complete documentation of ADR report of unusual failure in efficacy is retained for 25 years after the day on which they were created.

Appendix A

Glossary of Terms

The following definitions are provided to complement those already available under the glossary of terms in the current edition of the Canada Vigilance (MHPD) *Guidance Document for Industry – Reporting Adverse Reactions to Marketed Health Products* (2009), the Inspection Strategy for Post-Market Surveillance and other related documents referenced in these documents.

Adverse Drug Reaction (ADR) - "A noxious and unintended response to a drug, which occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of an organic function." Note that, for new drugs marketed in Canada, reports of unusual failure in efficacy are considered to be a type of adverse reactions (AR) report. (C.01.001 (1))

Drug - "Any substance or mixture of substances manufactured, sold, or represented for use in (a) the diagnosis, treatment, mitigation, or prevention of a disease, a disorder, an abnormal physical state, or the symptoms thereof, in humans or animals, (b) restoring, correcting, or modifying organic functions in humans or animals, or (c) "disinfection" in premises in which food is manufactured, prepared, or kept." (Section 2 of the *Food and Drugs Act*)

Manufacturer - "Manufacturer" or "distributor" means a person, including an association or partnership, who under their own name, or under a trade-, design or word mark, trade name or other name, word or mark controlled by them, sells a food or drug. (A.01.010) Within the context of the PMRC inspection programme, MAH and importers are considered manufacturers as their name appears on the label and as such, are subject to PMRC inspections.

New Drug - "(a) a drug that contains or consists of a substance, whether as an active or inactive ingredient, carrier, coating, excipient, menstruum or other component, that has not been sold as a drug in Canada for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that substance for use as a drug..." (C.08.001) Generally, if a NOC was issued for a drug, then that drug is considered to be a "new drug", regardless of how long it has been on the market.

Notice of Compliance: A notification, issued pursuant to paragraph C.08.004(1)(a), indicating that a manufacturer has complied with sections C.08.002 or C.08.003 and C.08.005.1 of the *Food and Drug Regulations*. Notices of Compliance are issued to a manufacturer following the satisfactory review of a submission.

Periodic Safety Update Report (PSUR) - A practical and achievable mechanism for summarizing interval safety data, and for conducting an overall safety evaluation. It is a tool for 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. (ICH E2C(R1) guideline)

Qualified Health Care Professional - A person who is a member in good standing of a professional medical, nursing, pharmacists' or other health care practitioner association and entitled to provide health care under the laws of the jurisdiction in which the person is located, and other individuals retained by the MAH who have the appropriate health care education and therapeutic expertise.

Serious Adverse Drug Reaction - "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." (C.01.001 (1))

Serious Unexpected Adverse Drug Reaction - "A serious adverse drug reaction that is not identified in nature, severity or frequency in the risk information set out on the label of the drug." (C.01.001 (1))

Signal Detection: Many information sources may be combined to identify a signal-a preliminary indication of a product-related safety issue. Assessment consists of the scientific/medical review of multiple data sources to analyse risks and benefits, while determining the likelihood of the association between the reaction and the health product.

Summary Report - In accordance with the *Food and Drug Regulations*, the market authorization holder (MAH) must, on an annual basis and whenever requested by Health Canada, conduct a concise, critical analysis of the adverse drug reactions and serious adverse drug reactions to a drug and prepare a summary report in respect of the reports received during the previous twelve months or received during such period of time as Health Canada may specify. Annual summary reports may be submitted in the form of a Periodic Safety Update Report (PSUR) as defined by ICH E2C(R1) guideline.

Unusual Failure in Efficacy - Lack of efficacy has been considered an adverse drug reaction for many years in the Canadian *Food and Drug Regulations*. The underlying principle is that if a drug fails to produce the expected pharmacological or therapeutic benefit, there may be an adverse outcome for the patient, including a worsening of the condition for which the medication is being taken. One example of unusual failure is a previously well-stabilized condition that deteriorates when the patient changes to a different brand or receives a new prescription.

Appendix B

References

Justice Canada

Acts and regulations of Canada are available on Justice Laws Web Site.

1. *Food and Drugs Act*
2. *Food and Drug Regulations*

Health Canada and International Websites

Documents that relate to PMRC are available on Health Canada's Web Site

1. Compliance and Enforcement Policy (POL-0001).

2. Guidance Document for Industry – Reporting Adverse Reactions to Marketed Health Products (2011)

3. ICH Harmonised Tripartite Guideline, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs E2C (R1)

4. Inspection Strategy for Post-Market Reporting Compliance for Drugs (POL-0041)

5. International Conference on Harmonisation, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2A)

6. International Conference on Harmonisation, Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2D) (2003).

7. International Conference on Harmonisation, Pharmacovigilance Planning (ICH E2E) (2004)

8. PIC/S Annex 11: Computerised Systems, April 2007

9. Risk Classification for Post-Market Reporting Compliance Observations (GUI-0063)