



1 **Our Mandate:**

2 To promote good nutrition and informed use of drugs, food, medical devices and natural health products, and to maximize the
3 safety and efficacy of drugs, food, natural health products, medical devices, biologics and related biotechnology products in the
4 Canadian marketplace and health system.
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9 **Inspectorate Program**

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11 **Guidance Document**

12 **Post-Market Reporting Compliance (PMRC)**
13 **Guidelines**

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15 **GUI-0102**
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21 Supersedes:
22 Not applicable

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24 Date Issued:
25 XXXXXXXX

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27 Date of Implementation:
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34 **Disclaimer**

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

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76 **1.0 Introduction**

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

91
92 These guidelines on PMRC pertain to Division 1 (C.01.016 to C.01.020) and Division 8 (C.08.007(h) and
93 C.08.008(c)), of Part C of the *Food and Drug Regulations*. The guidelines were developed by Health
94 Canada and are designed to facilitate compliance by the regulated industry and to enhance consistency in the
95 application of the regulatory requirements.

96
97 The content of this document should not be regarded as the only interpretation of the *Food and Drug*
98 *Regulations*, nor does it intend to cover every conceivable case. Alternative means of complying with the
99 *Food and Drug Regulations* can be considered with the appropriate justification.

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101

102 **2.0 Purpose**

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

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110 **3.0 Scope**

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

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-pharmaceuticals,

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-biologics, including blood products and therapeutic and diagnostic vaccines,

118

-preventative vaccines (including immunization schedule vaccines, flu vaccines, and vaccines for
travel),

119

-medical gases, and

120

-radiopharmaceuticals.

121

122 This guide does not currently apply to:

123

-hard surface disinfectants,

- 124 -veterinary products,
- 125 -natural health products, and
- 126 -whole blood and blood components.

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

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130 **4.0 Regulation**

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

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135 **Prohibition - C.01.016**

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

139

140 **Serious Adverse Drug Reaction Reporting - C.01.017**

141

142 **Regulation**

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

- 147 (a) any serious adverse drug reaction that has occurred in Canada with respect to the drug; and
- 148 (b) any serious unexpected adverse drug reaction that has occurred outside Canada with respect
149 to the drug.

150

151 **Rationale**

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

157

158 **Interpretation**

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

163

164

165 **Adverse Reaction Reporting**

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167 **1.0 Procedures and processes**

- 168
- 169 1.1 MAHs and importers should have in place systems and procedures for the receipt, handling,
170 evaluation and reporting of ADRs that are adequate to effectively sustain ADR reporting
171 within 15 days of receipt to Health Canada of domestic serious unexpected ADRs, foreign

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

- 181
- 182 1.2 MAHs should have in place adequate procedures for adverse drug reaction receipt, handling,
183 evaluation and reporting and should include at the minimum the following:
184
- 185 1.2.1 Requirement to report within 15 calendar days of receipt by the manufacturer, reports
186 of serious adverse drug reactions occurring within Canada, and serious unexpected
187 adverse drug reactions occurring outside of Canada and any unusual failure in
188 efficacy for new drugs;
189
- 190 1.2.2 Address all the specific Canadian regulatory requirements, such as when notification
191 is required, definition of serious and non-serious reactions, retention of all records
192 associated with adverse drug reaction, etc.
193
- 194 1.2.3 Requirement to have a health care professional to evaluate and assess adverse drug
195 reaction reports, including the process to review ADRs;
196
- 197 1.2.4 Identifying the minimum criteria for submitting a case
198
- 199 1.2.5 Identifying key personnel who are responsible for forwarding the adverse drug
200 reactions reports to Health Canada;
201
- 202 1.2.6 Procedure on how adverse drug reactions are tracked/logged in;
203
- 204 1.2.7 Procedure on how the firm is to be notified of foreign serious unexpected drug
205 reactions;
206
- 207 1.2.8 Requirements and concise methodology to accurately assess an adverse drug reaction
208 report, which includes, but is not limited to: Patient Information, Description of ADR,
209 Drug Product(s) involved, etc.
210
- 211 1.2.9 The responsibilities for the final approval of complaint/adverse drug reaction
212 evaluation and appropriate follow-up;
213
- 214 1.2.10 Reference to the contact information for the appropriate
215 department/branch/directorate within Health Canada where reports are to be
216 submitted;
217
- 218 1.2.11 Requirement to effectively follow-up with case reports, to document all attempts to
219 obtain follow-up information and submit information to the appropriate
220 department/branch/directorate within Health Canada as it becomes available;

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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

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- 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 pharmacovigilance data from technical complaints and medical information enquiries have been appropriately recorded and classified, for example serious ADR, in the pharmacovigilance 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.

- 317 3.1.6.3 Multiples ADR reports of the same adverse drug reactions can be deleted
318 within the pharmacovigilance system and a copy of the record is maintained
319 allowing for auditing of the record in the future.
320
- 321 3.1.6.4 Documented procedure should be in place describing when ADR reports may
322 be logically deleted and the process to do so.
323
- 324 3.1.6.5 Record of why a case has been deleted should be retained.
325
- 326 3.1.7 Change in the assessment of ADRs
327
- 328 3.1.7.1 Upon receipt of additional follow-up information, ADR reports should be re-
329 evaluated.
330
- 331 3.1.7.2 All ADR reports that have been upgraded to serious are to be sent to Health
332 Canada within the prescribed timelines.
333
- 334 3.1.7.3 MAH should notify Health Canada when a ADR report that was submitted to
335 Health Canada has been downgraded to non-serious.
336
- 337 3.1.7.4 Rationale for upgrading or downgrading an ADR report should be
338 documented.
339
- 340 4. Reporting of ADR data
341
- 342 4.1 Market Authorisation Holder
343
- 344 4.1.1 All ADRs that meet the requirements of the *Food and Drug Regulations* must be
345 reported to the MHPD in accordance with the *Food and Drug Regulations*.
346
- 347 4.1.2 Periodic checks are performed to ensure that the appropriate ADR reports are sent to
348 Health Canada.
349
- 350 4.1.3 Periodic checks are performed to ensure that the appropriate data is entered in the
351 system, safety database.
352
- 353 4.2 Importers
354
- 355 4.2.1 All suspected ADRs received are sent to the MAH, and should therefore be reported
356 to MHPD by the MAH.
357
- 358 5. Literature Search
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- 360 5.1 Market Authorisation Holder
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- 362 5.1.1 Procedure should be in place describing the process to perform literature searches, including
363 but not limited to how the search is done, the database used, and the periodicity of those
364 searches.
365

- 366 5.1.2 Searches, on the drug and active pharmaceutical ingredients, in published literature are
367 performed on a regular basis.
368
- 369 5.1.3 ADRs found during literature searches are classified according to their seriousness and
370 expectedness. These assessments are retained and well documented.
371
- 372 5.1.4 ADR reports from the scientific and medical literature must be reported to the MHPD in
373 accordance with the Food and Drug Regulations. For additional information, refer to
374 MHPD's document entitled "Guidance Document for Industry - Reporting Adverse
375 Reactions to Marketed Health Products"
376
- 377 5.1.5 Results of the literature searches are documented.
378
- 379 5.1.6 When literature search is performed by a third party, contractual agreements describing each
380 party responsible should exist.
381
- 382 6. Self-inspection program
383
- 384 6.1 A self-inspection program that covers all departments that may receive ADR reports or that
385 are involved in pharmacovigilance activities may help to ensure compliance with the appropriate
386 sections of the *Food and Drug Regulations* applicable to adverse drug reaction reporting.
387 Self-inspection programs should be in place and should include;
388
- 389 6.1.1 A comprehensive written procedure that describes the functions of the self-inspection
390 program
391
- 392 6.1.2 Periodic self-inspections that are carried out at defined frequencies, which are
393 documented.
394
- 395 6.1.3 Reports on the findings of the self-inspections and on corrective actions. These
396 reports should be reviewed by appropriate senior company management. Corrective
397 actions should be implemented in a timely manner.
398
- 399 6.2 Self-inspections that are conducted by personnel independent from the pharmacovigilance
400 department are suitably qualified to perform and evaluate the inspections.
401

402 Personnel and Training

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- 404 7. Market Authorisation Holder and Importers
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- 406 7.1 The individual in charge of the pharmacovigilance department:
407
- 408 7.1.1 is a qualified healthcare professional with pertinent training, and expertise to conduct
409 pharmacovigilance duties;
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- 411 7.1.2 Delegates duties to a qualified healthcare professional with pertinent training and
412 expertise to conduct pharmacovigilance duties.
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- 414 7.2 The Qualified healthcare professional;

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- 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,

- 463 8.1.4 processes by which an exchange of safety information, including timelines and
464 regulatory reporting responsibilities, are taking place between the manufacturer and
465 its partners (including, but not limited to, consultants and contractors).
466
- 467 8.1.5 to notify other party if changes to procedures are made, and
468
- 469 8.1.6 timeframes for exchange of information.
470
- 471 8.2 In the case of foreign manufacturers, the contractual agreement should specify to send
472 foreign serious and unexpected ADR case reports to the MAH in a timely manner so as to
473 promote compliance with regulatory reporting obligations.
474
- 475 8.3 In the case where the importer is responsible for the pharmacovigilance activities, the
476 contractual agreement should specify that the foreign MAH is to send the ADR data in a
477 timely manner.
478
- 479 8.4 All records (including, but not limited to, contracts and safety data/ADR data) are available
480 on the premises of the MAH and the importer.
481
- 482 8.5 When there is a transfer of market authorization/mergers, contractual agreement should exist
483 between the previous manufacturer and the new one outlining each party responsibility.
484
- 485 8.6 Contractual agreement is shared and signed off by each party.
486
- 487 8.7 Contractual agreement are to be reviewed periodically in order to reflect current regulations
488 and practices.
489

490 **Validation of Computerized Systems**

- 491
- 492 9. Market Authorisation Holder, Importer, and all parties involved in pharmacovigilance activities who
493 use an electronic system
494
- 495 9.1 Data of the validation of system(s) used for recording, evaluating, and tracking complaints
496 and ADRs should be available.
497
- 498 9.2 Computerized systems are validated, and spreadsheets to track ADRs are qualified and
499 system are periodically and suitably backed up at predefined intervals.
500
- 501 9.3 Validation is periodically reviewed at predefined intervals to assess the current suitability of
502 systems and past and proposed changes.
503

504 **Product Complaints**

505 10. Market Authorisation Holder and Importers

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- 508 10.1 Written procedures should be in place describing the handling of all complaints regarding a
509 drug product.
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- 511 10.2 The procedure should include:

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- 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

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

564
565 **Interpretation**

566
567 Note: The MAH is responsible for this section of the *Food and Drug Regulations*. Importers who have been
568 delegated that responsibility by the foreign MAH are also required to meet the requirements in this section.
569 All importers should have available evidence that the below requirements were met.

- 570
- 571 1. Written procedure for the preparation of the annual summary report (ASR) which includes, but is not
572 limited to:
 - 573
 - 574 1.1 A requirement to submit the ASR upon request to Health Canada within the time frame
575 specified by the Minister when the report is requested
 - 576
 - 577 1.2 The sections that should be included in the summary report as defined in Section 5.1 of
578 MHPD's guidance document entitled *Guidance Document for Industry - Reporting Adverse*
579 *Reactions to Marketed Health Products*
 - 580
 - 581 1.3 List of pertinent cases that are to be included in the summary report.
 - 582
 - 583 1.3 A requirement to prepare a summary report on an annual basis for each drug.
 - 584
 - 585 1.4 Documentation on what "annual" dates are used for preparing the ASR.
 - 586
 - 587 2. The MAH prepares an ASR of all information relating to adverse drug reactions and serious adverse
588 drug reactions to the drug that it received or became aware of during the previous 12 months. This
589 report should include foreign and domestic adverse drug reactions. It should also include expected
590 and unexpected adverse drug reactions as well as all adverse drug reactions related to unusual failure
591 in efficacy of a new drug.
 - 592
 - 593 3. The ASR contains a concise, critical analysis of the adverse drug reactions and serious adverse drug
594 reactions to the drug and recommended actions.
 - 595
 - 596 4. In preparing the annual summary report, the MAH shall determine, on the basis of the analysis,
597 whether there has been a significant change in what is known about the risks and benefits of the drug
598 since the last annual summary report, and shall include its conclusions in this regard in the summary
599 report.
 - 600
 - 601 5. If the MAH advises MHPD when it concludes from the ASR that there is a significant change in
602 what is known about the risks and benefits of a product relating to its safe use, information
603 (including notification of this information to MHPD, without delay) is available on file. The MAH
604 must notify the Minister without delay, in writing, if in preparing the annual summary report the
605 MAH concludes that there has been a significant change.
 - 606
 - 607 6. For the purposes of assessing the safety and effectiveness of the drug, the Minister may request in
608 writing that the MAH submit in the time period specified by the Minister:

- 609 (a) the annual summary reports;
610 (b) the case reports relating to the adverse drug reactions and serious adverse drug reactions
611 to the drug that are known to the MAH .
612
- 613 6.1 Requests for information from Health Canada are maintained.
614
- 615 7. If the MAH chooses to use a third party to prepare the ASR, contracts must be in place defining their
616 respective responsibilities.
617
- 618 8. Annual summary report reviewed by Health Canada and for which comments were received by the
619 MAH should be documented and changes implemented in subsequent summary report.
620
- 621 9. Verifications should be performed to ensure the accuracy and completeness of data/ information in
622 the summary report. There checks should be documented.
623
- 624 10. Signal detection
625
- 626 10.1 Written procedure should be in place that adequately describes the way in which the MAH
627 perform signal detection.
628
- 629 10.2 Roles and responsibilities of each person involved in the signal detection process are clearly
630 identified and documented.
631
- 632 10.3 The source of the information to include in the analysis and the method used for signal
633 detection should be documented.
634
- 635 10.4 Actions taken based on the outcome generated from the signal detection activities should be
636 documented adequately and include but not limited to the outcome, decision and actions.
637
- 638 10.5 Data regarding the potential significant change in the risks and benefits of the drugs should
639 be sent to Health Canada and should be documented.
640
- 641 11. Product Monograph (PM), label and leaflet
642
- 643 11.1 The person who assesses ADR has access to the latest approved label and product
644 monograph
645
- 646 11.2 Product information is kept up to date.
647
- 648 11.3 One copy of previous PMs, leaflets and labels are available on file.
649
- 650 11.4 Records are maintained of requests received from Health Canada to update product
651 information documents, if applicable.
652
- 653 11.5 Once a new safety issue has been identified and drug product information is to be updated,
654 procedures should be in place to facilitate timely submission of changes to ensure there is no
655 undue delay in updating documents.
656
657

658 12. Risk Management Plan (RMP)

659

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

663

664 12.1 RMP should be prepared in accordance with the Notice of compliance with conditions and
665 include at the minimum the following:

666

667 12.1.1 what will be done to monitor, including completed studies, on-going studies and
668 progress, any identified or potential risk and how more information will be gathered
669 (pharmacovigilance plan)

670

671 12.1.2 a description of the measures that will be required to minimise the risk for each
672 identified and potential risk mentioned in the safety specification (risk minimisation)

673

674 12.1.3 it should be product-specific

675

676 12.1.4 a plan to monitor the success of risk-minimisation activities and expectations on
677 acceptance criteria for success should be in place

678

679

680 **Issue-related Summary Report - C.01.019**

681

682 **Regulations**

683

684 **C.01.019**

685

686 (1) The Minister may, for the purposes of assessing the safety and effectiveness of the drug, request in
687 writing that the manufacturer submit to the Minister an issue-related summary report.

688

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

693

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

698

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

700

701 **Rationale**

702

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

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

708
709 **Interpretation**

710
711 Note: The MAH is responsible for this section of the *Food and Drug Regulations*. Importers who have been
712 delegated that responsibility by the foreign MAH are also required to meet the requirements in this section.
713 All importers should have available evidence that the below requirements were met.

- 714
715
- 716 1. Written procedure for the preparation of an issue-related summary report upon request from the
717 Minister which includes but is not limited to:
 - 718
719 1.1 A concise, critical analysis of the adverse drug reactions and serious adverse drug reactions
720 to the drug and case reports of all or specified adverse drug reactions and serious adverse
721 drug reactions to the drug that are known to the MAH in respect of the issue that the
722 Minister directs the MAH to analyse in the report.
 - 723
724 1.2 The maintenance of the issue-related summary report prepared by the MAH .
 - 725
726 2. A process should be established for the accurate and timely retrieval and output of stored data or
727 records from the pharmacovigilance system.
- 728
729

730 **Maintenance of Records - C.01.020**

731
732 **Regulation**

- 733
- 734 (1) The manufacturer shall maintain records of the reports and case reports referred to in sections
735 C.01.017 to C.01.019.
 - 736
737 (2) The manufacturer shall retain the records for 25 years after the day on which they were created.
- 738

739 **Rationale**

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

744
745 **Interpretation**

746
747 Note: Importers who have been delegated the activities related to pharmacovigilance by the foreign MAH
748 are also required to meet the requirements in this section. All importers should have available evidence that
749 the below requirements were met.

750
751 All relevant pharmacovigilance documents (such as associated records of actions taken or conclusions
752 reached) and standard operational procedures (SOP) are prepared by the relevant department. No changes
753 are made without the approval of the qualified person in charge of the pharmacovigilance. Any alteration

- 754 made to a document is signed and dated; the alteration permits the reading of the original information.
755 Where appropriate, the reason for the change is recorded.
756
757 Any documentation requested for evaluation by Health Canada is provided in one of the official languages.
758
759 1. Market Authorisation Holder and Importers
760
761 1.1 Records of serious ADR and annual summary reports maintained by MAH are accessible
762 within 72 hours from the MAH
763
764 1.2. Records are retained for a minimum of 25 years after the day on which they were created.
765
766 1.3 A procedure describes how ADR records are maintained, i.e., name of the filing system or
767 electronic database which would facilitate the management of any such records in a reliable
768 manner that allows for consistent retrieval.
769
770 1.4 Complete records, such as documentation of decisions, documentation of follow-up and
771 follow-up attempts and annual summary reports, are available in ADR files.
772
773 1.5 All computer systems should have in place a security system that prevents unauthorized
774 access and changes to the data.
775
776 1.6. A list of individuals who are authorised to access the system and make data changes should
777 be maintained.
778
779 2. The MAH retained all ADR records.
780
781 3. The importer retains at the minimum the following documents (depending on their responsibilities) :
782
783 3.1 Evidence that ADRs were sent to Health Canada
784
785 3.2 Evidence that summary reports were prepared on an annual basis, including date of issuance,
786 summary and conclusions.
787
788

789 **New Drugs – C.08.007 (h) and C.08.008 (c)**
790

791 **Regulation**
792

793 C.08.007 (h)
794

795 Where a manufacturer has received a notice of compliance issued in respect of a new drug submission or
796 abbreviated new drug submission or a supplement to either submission, the manufacturer shall establish and
797 maintain records, in a manner that enables an audit to be made, respecting...

798 (h) any unusual failure in efficacy of that new drug.
799

800 C.08.008 (c)
801

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

806

807 **Rationale**

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

814

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

819

820 **Interpretation**

821

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

825

- 826 1. The MAH has systems and procedures in place to receive, evaluate and report to Health Canada
827 within 15 days of the receipt of the information, any unusual failure in efficacy report of new drugs
828 marketed in Canada.
829
- 830 2. The MAH has identified products with new drug status. A new drug is a drug which received a
831 NOC (Notice of Compliance).
832
- 833 3. Criteria defining what is considered an unusual failure in efficacy of a new drug are established by
834 the MAH.
835
- 836 4. Every ADR report related to unusual failure in efficacy that meets the established criteria for
837 reporting unusual failure in efficacy is submitted to Health Canada within the appropriate timeframe
838 (i.e., within 15 days).
839
- 840 5. Qualified personnel (i.e., a qualified health care professional evaluates potential cases of unusual
841 failure in efficacy to determine if the case qualifies for expedited (15-day) reporting. These
842 evaluations and assessments are adequately documented.
843
- 844 6. The complete documentation of ADR reports of unusual failure in efficacy is available for auditing
845 purposes at the MAH premises or is easily accessible within 72 hours.
846
- 847 7. The complete documentation of ADR report of unusual failure in efficacy is retained for 25 years
848 after the day on which they were created.

849 Appendix A

850

851 **Glossary of Terms**

852

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

857

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

862

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

868

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

874

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

880

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

885

886 **Periodic Safety Update Report (PSUR)** - A practical and achievable mechanism for summarizing interval
887 safety data, and for conducting an overall safety evaluation. It is a tool for MAHs to conduct systematic
888 analyses of safety data on a regular basis. In addition to covering ongoing safety issues, the PSUR should
889 also include updates on emerging and/or urgent safety issues, and major signal detection and evaluation that
890 are addressed in other documents. (ICH E2C(R1) guideline)

891

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

896

897 **Serious Adverse Drug Reaction** - "A noxious and unintended response to a drug that occurs at any dose
898 and that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital
899 malformation, results in persistent or significant disability or incapacity, is life-threatening or results in
900 death." (C.01.001 (1))

901
902 **Serious Unexpected Adverse Drug Reaction** - "A serious adverse drug reaction that is not identified in
903 nature, severity or frequency in the risk information set out on the label of the drug." (C.01.001 (1))

904
905 **Signal Detection:** Many information sources may be combined to identify a signal-a preliminary indication
906 of a product-related safety issue. Assessment consists of the scientific/medical review of multiple data
907 sources to analyse risks and benefits, while determining the likelihood of the association between the
908 reaction and the health product.

909
910 **Summary Report** - In accordance with the *Food and Drug Regulations*, the market authorization holder
911 (MAH) must, on an annual basis and whenever requested by Health Canada, conduct a concise, critical
912 analysis of the adverse drug reactions and serious adverse drug reactions to a drug and prepare a summary
913 report in respect of the reports received during the previous twelve months or received during such period of
914 time as Health Canada may specify. Annual summary reports may be submitted in the form of a Periodic
915 Safety Update Report (PSUR) as defined by ICH E2C(R1) guideline.

916
917 **Unusual Failure in Efficacy** - Lack of efficacy has been considered an adverse drug reaction for many
918 years in the *Canadian Food and Drug Regulations*. The underlying principle is that if a drug fails to
919 produce the expected pharmacological or therapeutic benefit, there may be an adverse outcome for the
920 patient, including a worsening of the condition for which the medication is being taken. One example of
921 unusual failure is a previously well-stabilized condition that deteriorates when the patient changes to a
922 different brand or receives a new prescription.

923 Appendix B

924 **References**

925

926 **Justice Canada**

927

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

929

930 1. *Food and Drugs Act*

931 2. *Food and Drug Regulations*

932

933 **Health Canada and International Websites**

934

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

936

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

938

939 2. Guidance Document for Industry – Reporting Adverse Reactions to Marketed Health Products
940 (2011)

941

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

944

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

946

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

949

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

952

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

954

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

956

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