



3 **Our Mandate:**

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

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11 **Guidance Document**

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13 **Risk Classification of Post-Market Reporting**
14 **Compliance Observations**
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17 **GUI-0063**

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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*
36 *in the event of any inconsistency or conflict between that Act or Regulations and this document, the Act or*
37 *the Regulations take precedence. This document is an administrative document that is intended to facilitate*
38 *compliance by the regulated party with the Act, the Regulations and the applicable administrative policies.*
39 *This document is not intended to provide legal advice regarding the interpretation of the Act or*
40 *Regulations. If a regulated party has questions about their legal obligations or responsibilities under the*
41 *Act or Regulations, they should seek the advice of legal counsel.*
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71 **1.0 Purpose**

72
73 To classify the observations noted during Post-Market Reporting Compliance (PMRC) drug
74 inspections to their risk.

75
76 To ensure uniformity among the inspectors of Health Canada (Inspectorate Program) in the attribution
77 of the rating following Post-Market Reporting Compliance drug inspections.

78
79 To inform the industry of the situations that Health Canada considers unacceptable and that will
80 generate a non-compliant rating (NC) following a Post-Market Reporting Compliance drug inspection.

81
82 **2.0 Background**

83
84 During PMRC drug inspections, deviations from the *Food and Drug Regulations*, more specifically
85 sections C.01.016 to C.01.020, and C.08.007 and C.08.008, and the current edition of the *Post-Market*
86 *Reporting Compliance Guidelines* (GUI-0102) are noted by the inspector. These deviations appear as
87 observations on the inspection Exit Notice. An assessment of these observations is then completed by
88 the inspector who assigns a risk to each observation based on this guidance document. Subsequently,
89 an overall compliance rating is attributed to the inspected site. The possible ratings are defined below:

90
91 C (Compliant) - At the time of the inspection, the regulated party has demonstrated that the
92 activities it conducts are in compliance with the Food and Drugs Act and its associated
93 Regulations. A “C” rating does not mean that there are no observations or corrective actions
94 required.

95
96 NC (Non-Compliant) - At the time of the inspection, the regulated party has not demonstrated
97 that the activities it conducts are in compliance with the Food and Drugs Act and its associated
98 Regulations.

99
100 It is recognized that the evaluation of the conformity of manufacturers, which includes Market
101 Authorization Holders (MAH) and importers in the context of this inspection programme with their
102 regulatory responsibilities should commensurate with the risk involved taking into account the nature
103 and extent of the deviation. Nonetheless, generally, situations involving fraud, misrepresentation or
104 falsification of drug safety data will generate a NC rating, irrespective of the category of products
105 involved.

106
107 The assignment of a NC rating may have serious consequences for an establishment. These
108 consequences may include the implementation of immediate corrective measures to the seizure and
109 detention of drug products to the suspension and the cancellation of marketing authorization.
110 Therefore, these situations of non-conformity have to be well defined, unambiguous and directly
111 supported by the applicable sections of the *Food and Drug Regulations*.

112
113 **3.0 Scope**

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115 The *Food and Drug Regulations* set forth regulatory requirements for manufacturers to report adverse
116 drug reactions and to report unusual failure in efficacy of new drugs to Health Canada. This guide

117 covers the following drugs marketed in Canada for human use which are subject to the above
118 requirements of the *Food and Drug Regulations*:
119 · pharmaceuticals,
120 · biologics, including blood products and therapeutic and diagnostic vaccines,
121 · preventative vaccines (including immunization schedule vaccines, flu vaccines, and
122 vaccines for travel),
123 · medical gases, and
124 · radiopharmaceuticals.

125
126 This guide does not currently apply to:

- 127 · hard surface disinfectants,
- 128 · veterinary products,
- 129 · natural health products, and
- 130 · whole blood and blood components.

131

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

134

135 Appendix 1 of this document describe the observations related to each category of risk. Please note
136 that the list of observations in the appendix is not exhaustive and that additional observations may be
137 added where appropriate.

138

139 The numbering system assigned to each section in the appendix is a reference to the applicable
140 regulations as per the current edition of the *Post-Market Reporting Compliance Guidelines* (GUI-
141 0102).

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143

144 **4.0 Guide**

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146 **4.1 Assignment of the Risk to an Observation**

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148 Whereas it is recognized that it is impossible to encompass every situation that may generate a risk, the
149 following principles should be considered:

150

- 151 · The risk assigned will be in relation to the nature of the deviation as well as the number of
152 occurrences.

153

- 154 · Where a Risk 2 observation is re-evaluated as a Risk 1 (Risk 2 observation with an arrow), this
155 situation is immediately brought to the attention of the company's officials; proper explanation
156 will be provided to the establishment.

157

158 **4.2 Assignment of the Inspection Rating**

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160 The overall inspection rating assigned is based on the risk involved by taking into account the nature
161 and extent of the deviations as well as the type of product involved and the impact on health and safety
162 of the patient.

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164 Generally, a NC rating is assigned when a Risk 1 observation is noted during an inspection.

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Such a situation is immediately brought to the attention of the company's officials. The Inspectorate program management is notified in a timely manner as well.

Where in the opinion of the inspector the resulting products present a significant health risk, appropriate enforcement actions may be initiated.

A NC rating may also be assigned in the following situations:

- When numerous Risk 2 observations are noted during an inspection indicating that the company did not control its processes and operations sufficiently.
- When numerous occurrence of similar Risk 2 observations are noted during a PMRC inspection indicating that the company did not have a system in place to provide for ongoing process improvement
- Repetition of many Risk 2 and Risk 3 observations noted during previous inspections indicating that the company did not:
 - implement the corrective actions submitted following the previous inspection or
 - did not put in place adequate preventive actions in a timely manner to avoid recurrence of such deviations.

Generally, a C rating is assigned when Risk 2 observations are noted and in all situations where only Risk 3 observations are noted during an inspection.

4.3 Additional Guidance

When a NC rating is assigned, the inspector will issue a draft Inspection Exit Notice during the exit meeting. The draft inspection Exit Notice will be reviewed for quality assurance purposes before the final report is issued to an establishment.

When observations leading to a NC rating are made, the Inspection Exit Notice could be issued with a C rating if, during the inspection:

- the establishment immediately implements all necessary actions to resolve the cause(s) of the observation(s) leading to the NC rating and,
- sufficient assurance can be provided to prevent a recurrence.

In such instances, the risk assigned to the observation will remain the same.

If the management of the company wishes to dispute the results of the inspection report, they should contact the appropriate Inspectorate program regional manager.

206 **5.0 Associated Documents**

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208 **Justice Canada**

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

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- 212 1. *Food and Drugs Act*
- 213 2. *Food and Drug Regulations*

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217 ***Health Canada and International Websites***

218

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

220

- 221 1. Compliance and Enforcement Policy (POL-0001)
- 222
- 223 2. Guidance Document for Industry – Reporting Adverse Reactions to Marketed Health Products
- 224 (2011)
- 225
- 226 3. ICH Harmonised Tripartite Guideline, Clinical Safety Data Management: Periodic Safety Update
- 227 Reports for Marketed Drugs E2C (R1)
- 228
- 229 4. Inspection Strategy for Post-Market Reporting Compliance for Drugs (POL-0041)
- 230
- 231 5. PIC/S Annex 11: Computerised System
- 232
- 233 6. Risk Classification for Post-Market Reporting Compliance Observations (GUI-0063)

234 **Appendix 1**

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236 **Glossary of Terms**

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238 The following definitions are provided to complement those already available under the glossary of
239 terms in the current edition of the Canada Vigilance (MHPD) *Guidance Document for Industry –*
240 *Reporting Adverse Reactions to Marketed Health Products* (2011), the *Inspection Strategy for Post-*
241 *Market Reporting Compliance* (POL-0041) and the *Post-Market Reporting Compliance Guidelines*
242 (GUI-0102) or other related documents referenced in these documents.

243

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

248

249 **Observation** - A deviation from or deficiency based on the Food and Drug Regulations pertaining to
250 reporting of adverse drug reactions (ADR) and unusual failure in efficacy of new drugs noted by an
251 inspector during the inspection of a drug establishment that is confirmed in writing to the company in
252 the Exit Notice. The observations are classified as "Critical", "Major" and "Other" and are assigned a
253 risk classification, ranging from Risk 1 (critical) to Risk 2 (major) to Risk 3 (other).

254

255 **Critical observation (Risk 1):**

256 Observation of a critical deviation from the *Food and Drug Regulations* that describes a
257 situation that may produce an immediate or latent health risk as a result of the absence of drug
258 safety information. Observations that involve fraud, misrepresentation or falsification under the
259 Food and Drugs Act and its associated Regulations of data are also considered critical.

260

261 Refer to Appendix 1 for the list of observations which the Inspectorate program considers
262 critical and which will be assigned a Risk 1.

263

264 **Major observation (Risk 2):**

265 Observation of a major deviation from the *Food and Drug Regulations* that describes a
266 situation of incomplete drug safety information that may result in a latent health risk.

267

268 Refer to Appendix 1 for the list of observations that are considered major and which will be
269 assigned a Risk 2. Certain Risk 2 observations may be upgraded to Risk 1. These observations
270 are indicated with an arrow (↑); although it does not preclude other Risk 2 observations to be
271 upgraded depending on the nature and the extent of the observation.

272

273 **Other observation (Risk 3):**

274 Observation that describes a deviation from the Food and Drug Regulations that is neither
275 critical nor major.

276

277 Observations that are neither critical nor major are considered as "other" and will be assigned a
278 Risk 3. All Risk 3 observations could be upgraded to Risk 2 depending on the situation. Refer
279 to Appendix 1 for the list.

280

281 **Manufacturer** - "Manufacturer" or "distributor" means a person, including an association or
282 partnership, who under their own name, or under a trade-, design or word mark, trade name or other
283 name, word or mark controlled by them, sells a food or drug. (A.01.010) Within the context of the
284 PMRC inspection programme, MAH and importers are considered manufacturers as their name
285 appears on the label and as such, are subject to PMRC inspections.
286

287 **New Drug** - "(a) a drug that contains or consists of a substance, whether as an active or inactive
288 ingredient, carrier, coating, excipient, menstruum or other component, that has not been sold as a drug
289 in Canada for sufficient time and in sufficient quantity to establish in Canada the safety and
290 effectiveness of that substance for use as a drug..." (C.08.001)
291 Generally, if a NOC was issued for a drug, then that drug is considered to be a "new drug", regardless
292 of how long it has been on the market.
293

294 **Periodic Safety Update Report (PSUR)** - A practical and achievable mechanism for summarizing
295 interval safety data, and for conducting an overall safety evaluation. It is a tool for MAHs to conduct
296 systematic analyses of safety data on a regular basis. In addition to covering ongoing safety issues, the
297 PSUR should also include updates on emerging and/or urgent safety issues, and major signal detection
298 and evaluation that are addressed in other documents. (ICH E2C(R1) guideline)
299

300 **Serious Adverse Drug Reaction** - "A noxious and unintended response to a drug that occurs at any
301 dose and that requires in-patient hospitalization or prolongation of existing hospitalization, causes
302 congenital malformation, results in persistent or significant disability or incapacity, is life-threatening
303 or results in death." (C.01.001 (1))
304

305 **Serious Unexpected Adverse Drug Reaction** - "A serious adverse drug reaction that is not identified
306 in nature, severity or frequency in the risk information set out on the label of the drug." (C.01.001 (1))
307

308 **Summary Report** - In accordance with the Food and Drug Regulations, the market authorization
309 holder (MAH) must, on an annual basis and whenever requested by Health Canada, conduct a concise,
310 critical analysis of the adverse drug reactions and serious adverse drug reactions to a drug and prepare
311 a summary report in respect of the reports received during the previous twelve months or received
312 during such period of time as Health Canada may specify. Annual summary reports may be submitted
313 in the form of a Periodic Safety Update Report (PSUR) as defined by ICH E2C(R1) guideline.
314

315 **Unusual Failure in Efficacy** - This has been considered an adverse reaction for many years under the
316 Food and Drug Regulations. It applies to new drugs only. The underlying principle is that if a health
317 product fails to produce the expected intended effect, there may be an adverse outcome for the patient,
318 including an exacerbation of the condition for which the health product is being used. Clinical
319 judgment should be exercised by a qualified health care professional from the market authorization
320 holder (MAH) to determine if the problem reported is related to the product itself, rather than one of
321 treatment selection or disease progression since health products cannot be expected to be effective in
322 100% of the patients. One example of unusual failure in efficacy is a previously well-stabilized
323 condition that deteriorates when the patient changes to a different brand or receives a new prescription.
324 Another example of a case that should be reported on an expedited basis is a life-threatening infection
325 where the failure in efficacy seems to be due to the development of a newly resistant strain of
326 bacterium previously regarded as susceptible.
327

328 **Appendix 2**

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330 **Serious Adverse Drug Reaction Reporting C.01.017**

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332 **Risk 1 (Critical) Observations**

- 333 · None of the domestic serious unexpected adverse drug reactions received are reported to Health
- 334 Canada by the manufacturer
- 335 · None of the foreign serious unexpected adverse drug reactions received are reported to Health
- 336 Canada by the manufacturer
- 337 · Individual in charge of the Pharmacovigilance department is not a qualified healthcare
- 338 professional
- 339

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340 **Risk 2 (Major) Observations**

- 341 · None of the domestic serious expected adverse drug reactions received are reported to Health
- 342 Canada by the MAH (↑)
- 343 · Less than the total number of domestic serious expected adverse reaction reports and domestic
- 344 serious unexpected adverse reaction reports received by the MAH are reported to Health
- 345 Canada (↑)
- 346 · Less than the total number of foreign serious unexpected adverse reaction reports received by
- 347 the manufacturer are reported to Health Canada (↑)
- 348 · Domestic serious adverse drug reactions are not reported within 15 calendar days of the receipt
- 349 of the reports by the manufacturer (↑)
- 350 · Foreign serious unexpected adverse drug reactions are not reported within 15 calendar days of
- 351 the receipt of the reports by the manufacturer (↑)
- 352 · No written procedure for reporting any serious adverse reactions that occurred in Canada or any
- 353 unexpected adverse reaction that occurred outside Canada within 15 days of receiving the
- 354 information to Health Canada in accordance with the requirements of section C.01.017 of the
- 355 Food and Drugs Regulations.
- 356 · Lack of systems and procedures for the receipt, handling, evaluation and reporting of ADRs
- 357 that are adequate to effectively sustain ADR reporting within 15 days of receipt to Health
- 358 Canada of domestic serious unexpected ADRs, foreign serious unexpected ADRs, and domestic
- 359 serious expected ADRs, as well as any follow-up information for initial case reports. (↑)
- 360 · ADR reports are not coded using the Medical Dictionary for Regulatory Activities (MedDRA)
- 361 terminology.
- 362 · No documented rationale for the deletion of duplicate reports.
- 363 · Duplicate ADR reports are deleted without the proper approval
- 364 · Rationale is not documented for the downgrading of serious ADR
- 365 · No written procedure describing the process to perform literature searches
- 366 · Delegation of responsibilities for Pharmacovigilance activities to insufficiently qualified
- 367 persons.
- 368 · Insufficient training for personnel involved in pharmacovigilance activities resulting in related
- 369 PMRC deviations.
- 370 · Consultant or contractor does not have necessary qualifications, training, and experience to
- 371 advise on the subjects for which they are retained.
- 372 · Lack of adequate contractual or licensing agreements in place to specify the processes by which
- 373 an exchange of adverse reaction information, including timelines and regulatory reporting
- 374 responsibilities, are taking place between the MAH/importer and its partners (e.g., global
- 375 headquarters)

- 376 · Systems used for recording, evaluating, and tracking complaints and ADRs are not validated.
- 377 · Lack of or inadequate system for complaint handling.
- 378 · Lack of or inadequate system for self-inspection program that covers all departments that may
- 379 receive ADR reports or that are involved in pharmacovigilance activities

380

381 **Risk 3 (Other) Observations**

- 382 · Follow-up information for initial case reports was not sought and submitted as information
- 383 became available
- 384 · No documented evidence that the system for recording complaints had been validated.
- 385 · A comprehensive procedure and system for the receipt, evaluation and reporting of adverse
- 386 drug reactions, the preparation of annual summary reports and the retention of all related data
- 387 had not been formally defined and established.
- 388 · No training records available for the personnel in charge of receiving, evaluating and reporting
- 389 adverse drug reactions.
- 390 · Systems and procedures for the receipt handling, evaluation and reporting of ADRs are
- 391 deficient.
- 392 · No periodic checks of all pharmacovigilance data
- 393 · All suspected adverse drug reactions are not recorded and/or tracked appropriately.
- 394 · Results of literature searches are not documented and/or assessments of
- 395 seriousness/expectedness are not retained.
- 396 · The decision-making process to determine if a case is reportable inappropriately documented
- 397 · Inadequate training records.
- 398 · Insufficient written training program.
- 399 · Incomplete contractual agreement

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401

402 Annual Summary Report and Case Reports C.01.018

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404 **Risk 1 (Critical) Observations**

- 405 · No records of serious adverse drug reaction reports were accessible within 72 hours from the
- 406 manufacturer.

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408 **Risk 2 (Major) Observations**

- 409 · Not all records of serious adverse drug reaction reports were accessible within 72 hours from
- 410 the MAH.
- 411 · Annual summary reports of domestic serious adverse drug reactions and foreign serious
- 412 unexpected adverse drug reactions are not maintained by the MAH.
- 413 · Annual summary reports of domestic serious adverse drug reactions and foreign serious
- 414 unexpected adverse drug reactions are not prepared by the MAH.
- 415 · Case reports and summary reports have not been submitted within the time period specified by
- 416 Health Canada.
- 417 · Annual summary reports of domestic serious adverse drug reactions and foreign serious
- 418 unexpected adverse drug reactions are not prepared by the MAH.
- 419 · No written procedure for the preparation of the annual summary report.
- 420 · Significant change in what is known about the risks and benefits were not sent to Health
- 421 Canada.
- 422 · No contractual agreement with the outside agent responsible to prepare the annual summary
- 423 reports.

- 424 · Changes recommended by Health Canada were not documents and/or implemented in
- 425 subsequent summary reports.
- 426 · No quality control checks to ensure the accuracy and completeness of data/ information in the
- 427 summary report.
- 428 · Lack of or inadequate written procedure that describes the way in which the MAH perform
- 429 signal detection.
- 430 · Obsolete label used for the assessment of expectedness
- 431 · Risk management plans are not prepared in accordance with the Notice of compliance with
- 432 conditions, if applicable.
- 433

434 **Risk 3 (Other) Observations**

- 435 · The MAH has not included in the annual summary reports all domestic and foreign serious
- 436 adverse drug reactions, domestic and foreign non-serious unexpected adverse drug reactions
- 437 and domestic unusual failure in efficacy reports that were received
- 438 · Incomplete annual summary reports.
- 439
- 440

441 Issue-related Summary Report C.01.019

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443 **Risk 1 (Critical) Observations**

- 444 · The MAH or importer has not notified Health Canada when issue was found with a drug
- 445 product.
- 446

447 **Risk 2 (Major) Observations**

- 448 · No written procedure for the preparation of an issue-related summary report when a request is
- 449 received from Health Canada.
- 450

451 **Risk 3 (Other) Observations**

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454 Maintenance of Records C.01.020

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456 **Risk 1 (Critical) Observations**

- 457 · Evidence of falsification or misrepresentation of records.
- 458

459 **Risk 2 (Major) Observations**

- 460 · Lack of or inadequate procedure describing how ADR records are maintained.
- 461 · Records are not retained for a minimum of 25 years after the day on which they were created.
- 462 · Records of serious ADR and annual summary reports are not maintained by the MAH and/or
- 463 are accessible within 72 hours from the MAH.
- 464 · Lack of or incomplete records of complaints.
- 465 · No restricted access to ADR records
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467 **Risk 3 (Other) Observations**

- 468 · No organization charts.
- 469 · Incomplete records in adverse drug reactions files

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Risk 1 (Critical) Observations

- No records of reports domestic unusual failure in efficacy of new drugs were accessible within 72 hours from the MAH
- None of the reports of the domestic unusual failure in efficacy of new drugs received are reported to Health Canada by the MAH

Risk 2 (Major) Observations

- Not all records of domestic unusual failure in efficacy of new drugs were accessible within 72 hours from the MAH
- Less than the total number of reports received by the MAH of reports of domestic unusual failure in efficacy of new drugs are reported to Health Canada
- Domestic cases of unusual failure in efficacy of new drugs are not reported within 15 calendar days of the receipt of the reports by the MAH
- Lack of or inadequate systems and procedures in place for the receipt, evaluation and reporting to Health Canada within 15 days of the receipt of the information, of any unusual failure in efficacy report of new drugs marketed in Canada.
- Criteria defining what is considered an unusual failure in efficacy of a new drug are not established by the MAH.
- Complete documentation of ADR report of unusual failure in efficacy is not retained for 25 years after the day on which they were created.
- Assessments of suspected case of unusual failure in efficacy are not well documented

Risk 3 (Other) Observations