To: Associations and Stakeholders

Health Canada is implementing an inspection programme for post-market surveillance for drugs. The Health Products and Food Branch Inspectorate, in collaboration with the Marketed Health Products Directorate, will verify compliance of manufacturers (as defined in the Food and Drug Regulations section A.01.010) with the regulatory requirements pertaining to the reporting of adverse drug reactions and reporting of unusual failure in efficacy of new drugs to Health Canada.

I am pleased to inform you that the guidance document entitled “Risk Classification of Post-Market Surveillance Observations” is now available for comments on the Inspectorate website at:

http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate

Comments on the guidance document can be sent to the Inspectorate via fax at (613) 952-9805 or e-mail at postmarketsurveillance@hc-sc.gc.ca until August 31, 2004.

Original signed by
Diana Dowthwaite (for)

Jean Lambert
Director General
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.

DRAFT
Health Products and Food Branch Inspectorate

Guide-0063

Risk Classification of Post-Market Surveillance Observations

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Ce document est aussi disponible en français.
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1.0 PURPOSE

To classify the observations noted during post-market surveillance drug inspections to their risk.

To ensure uniformity among the inspectors of the Health Products and Food Branch Inspectorate (Inspectorate) in the attribution of the rating following post-market surveillance drug inspections.

To inform the industry of the situations that the Inspectorate considers unacceptable and that will generate a NC rating (defined below) following a post-market surveillance drug inspection.

2.0 BACKGROUND

During post-market surveillance drug inspections, deviations from the Food and Drug Regulations are noted by the inspector and are then recorded as observations in the Inspection Exit Notice. With the aid of this guide, a judgement is made of the observations and each observation is risk rated. Subsequently, an overall compliance rating is attributed to the inspected site. The possible compliance ratings are defined below:

C - No objectionable conditions or practices were observed with regards to regulatory requirements pertaining to reporting of adverse drug reactions and/or reporting of unusual failure in efficacy of new drugs

NC - Objectionable conditions or practices were observed with regards to regulatory requirements pertaining to reporting of adverse drug reactions and/or reporting of unusual failure in efficacy of new drugs

It is recognized that the evaluation of the conformity of manufacturers with their regulatory responsibilities should commensurate with the risk involved taking into account the nature and extent of the deviation. Nonetheless, generally, situations involving fraud, misrepresentation or falsification of drug safety data will generate a NC rating.

The assignment of a NC rating may have serious consequences for an establishment. These consequences may include the implementation of immediate corrective measures. Therefore, these situations of non-conformity have to be well defined, unambiguous and directly supported by the applicable Regulations.

The appendices attached to the present document describe the observations related to each category of risk. Please note that the list of observations in each appendix is not exhaustive and that additional observations may be added where appropriate.

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 drugs which are subject to the above requirements of the Food and Drug Regulations: pharmaceutical and biological drugs. Blood products and therapeutic and diagnostic vaccines are included in the scope of this guide. However, radiopharmaceuticals, veterinary drugs, natural health products and preventative vaccines, including immunization schedule vaccines, influenza vaccines and vaccines for travel, whole blood and blood components are excluded. In addition, this guide does not apply to adverse reaction reports resulting from drugs studied in a clinical trial where a Clinical Trial Application has been submitted to Health Canada.
4.0 DEFINITIONS

The following definitions are provided to complement those already available under the glossary of terms in the current edition of the Guidelines for Reporting Adverse Drug Reactions to Marketed Drugs, Guidelines for the Canadian Pharmaceutical Industry on Reporting Adverse Reactions to Marketed Drugs (Vaccines Excluded), Revised July 2001 and the Inspection Strategy for Post-Market Surveillance or other related documents referenced in these documents.

**Observation:**

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

**Critical observation:**

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

Appendix 1 lists observations that the Inspectorate considers critical. These observations will be assigned a Risk 1.

**Major observation:**

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

Appendix 2 lists observations that are considered major and which will be assigned a Risk 2. Certain Risk 2 observations may be upgraded to Risk 1, for example, if they are related to a new drug. These are indicated with an arrow (1).

**Other observation:**

Observation that describes a deviation from the *Food and Drug Regulations* that is neither critical or major.

Appendix 3 lists “Other” observations that will be assigned a Risk 3. Certain Risk 3 observations may be upgraded to Risk 2. These are indicated with an arrow (1).

**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 *(fabricant ou distributeur)* (A.01.010)

**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...” (*drogue nouvelle*) (C.08.001)

The Therapeutic Products Directorate, HPFB policy issue, New Drug - Sufficient Time (August 21, 1991), interprets the phrase "sufficient time" as a minimum of seven years from the initial date of marketing in Canada.

**Acronyms:**

ADR: Adverse Drug Reaction  
CECD: Compliance and Enforcement Coordination Division  
CTA: Clinical Trial Application  
EL: Establishment License  
GMP: Good Manufacturing Practices  
HPFB: Health Products and Food Branch  
IRS: Inspection Reporting System  
MHPD: Marketed Health Products Directorate, Health Products and Food Branch

**5.0 GUIDE**

**5.1 Assignment of the risk to an observation**

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

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

- Where a Risk 2 observation is re-evaluated as a Risk 1 (Risk 2 observation with an arrow), this situation is immediately brought to the attention of the company’s officials; proper explanation will be provided to the establishment and this explanation should be captured in the “Inspector’s Comments” field of the “Inspection Summary” in the Inspection Reporting System (IRS).

**5.2 Assignment of the inspection rating**

**5.2.1 Risk 1 observation:**

Generally, a NC rating is assigned when at least one Risk 1 observation is noted during an inspection. Such a situation is immediately brought to the attention of the company’s officials. The Inspectorate management is notified in a timely manner. Where in the opinion of the inspector the resulting products present a significant health hazard, the company is expected to address the issue immediately. Appropriate compliance and enforcement actions may be initiated according to the HPFB Compliance and Enforcement Policy (POL-0001).

**5.2.2 Risk 2 observation:**

Generally, a C rating is assigned when Risk 2 observations are noted during an inspection. However, a NC rating may be assigned in the following situations:

- When numerous Risk 2 observations are noted during an inspection indicating that the company does...
not sufficiently control its post-market surveillance activities.

- Repetition of many Risk 2 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.

5.2.3 Risk 3 observation:

A C rating is assigned in all situations where only Risk 3 observations are noted.

5.3 Additional guidance

When a NC rating is assigned, the inspector will issue a draft Inspection Exit Notice during the exit meeting. The final Exit Notice will be issued only after a review of the draft, in accordance with the usual practices of the Inspectorate.

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, the “Dispute resolution and appeals” mechanism described in the Good Manufacturing Practices (GMP) and Establishment Licensing (EL) Enforcement Policy POL-0004 should be followed.

6.0 REFERENCES

1. Health Products and Food Branch Inspectorate, Inspection Strategy for Post-Market Surveillance
3. Health Canada, Health Products and Food Branch Inspectorate, Good Manufacturing Practices (GMP) and Establishment Licensing (EL) Enforcement Directive, No. POL-0004
5. Health Products and Food Branch Compliance and Enforcement Policy, No. POL-0001
6. Health Products and Food Branch, Guidance for Clinical Trial Sponsors: Clinical Trial Applications, June 25, 2003
Appendix 1
Risk 1 (Critical) Observations

Adverse Drug Reaction Reporting C.01.016

- None of the domestic serious unexpected adverse drug reactions including those that occurred during studies not under a CTA (i.e. Phase IV clinical trials) received are reported to Health Canada by the manufacturer

- None of the foreign serious unexpected adverse drug reactions including those that occurred during studies not under a CTA (i.e. Phase IV clinical trials) received are reported to Health Canada by the manufacturer

Adverse Drug Reaction Reporting C.01.017

- No records of adverse drug reaction reports and serious adverse drug reaction reports are kept by the manufacturer for auditing purposes

New Drugs C.08.007

- No records of domestic unusual failure in efficacy of new drugs including those that occurred during studies not under a CTA (i.e. Phase IV clinical trials) are kept by the manufacturer for auditing purposes

New Drugs C.08.008

- None of the domestic unusual failure in efficacy of new drugs including those that occurred during studies not under a CTA (i.e. Phase IV clinical trials) received are reported to Health Canada by the manufacturer
Appendix 2
Risk 2 (Major) Observations

Adverse Drug Reaction Reporting C.01.016

- None of the domestic serious expected adverse drug reactions including those that occurred during studies not under a CTA (i.e. Phase IV clinical trials) received are reported to Health Canada by the manufacturer (1)

- Less than the total number of reports received by the manufacturer of domestic serious expected and unexpected adverse drug reactions including those that occurred during studies not under a CTA (i.e. Phase IV clinical trials) are reported to Health Canada

- Less than the total number of reports received by the manufacturer of foreign serious unexpected adverse drug reactions including those that occurred during studies not under a CTA (i.e. Phase IV clinical trials) are reported to Health Canada

- Domestic serious expected and unexpected adverse drug reactions including those that occurred during studies not under a CTA (i.e. Phase IV clinical trials) are not reported within 15 calendar days of the receipt of the reports by the manufacturer

- Foreign serious unexpected adverse drug reactions including those that occurred during studies not under a CTA (i.e. Phase IV clinical trials) are not reported within 15 calendar days of the receipt of the reports by the manufacturer

- Annual summary reports of domestic serious expected and unexpected adverse drug reactions, non-serious unexpected adverse drug reactions and unusual failure in efficacy for new drugs are not prepared by the manufacturer

- Annual summary reports of domestic serious unexpected adverse drug reactions and unusual failure in efficacy that occurred during studies not under a CTA (i.e. Phase IV clinical trials) are not prepared by the manufacturer

- Annual summary reports of foreign serious expected and unexpected adverse drug reactions, and non-serious unexpected adverse drug reactions are not prepared by the manufacturer

- Annual summary reports of foreign serious unexpected adverse drug reactions that occurred during studies not under a CTA (i.e. Phase IV clinical trials) are not prepared by the manufacturer

- Case reports and summary reports have not been submitted within 30 days after receiving the request from Health Canada

Adverse Drug Reaction Reporting C.01.017

- Records of adverse drug reaction reports and serious adverse drug reaction reports kept by the manufacturer for auditing purposes are incomplete
- Annual summary reports of domestic serious expected and unexpected adverse drug reactions, non-serious unexpected adverse drug reactions and unusual failure in efficacy reports for new drugs are not maintained by the manufacturer.

- Annual summary reports of domestic serious unexpected adverse drug reactions and unusual failure in efficacy for new drugs that occurred during studies not under a CTA (i.e. Phase IV clinical trials) are not maintained by the manufacturer.

- Annual summary reports of foreign serious expected and unexpected adverse drug reactions, and non-serious unexpected adverse drug reactions are not maintained by the manufacturer.

- Annual summary reports of foreign serious unexpected adverse drug reactions that occurred during studies not under a CTA (i.e. Phase IV clinical trials) are not maintained by the manufacturer.

**New Drugs C.08.007**

- Records of domestic unusual failure in efficacy of new drugs including those that occurred during studies not under a CTA (i.e. Phase IV clinical trials) kept by the manufacturer for auditing purposes are incomplete.

**New Drugs C.08.008**

- Less than the total number of reports received by the manufacturer of reports of domestic unusual failure in efficacy of new drugs including those that occurred during studies not under a CTA (i.e. Phase IV clinical trials) are reported to Health Canada.

- Domestic unusual failure in efficacy of new drugs including those that occurred during studies not under a CTA (i.e. Phase IV clinical trials) are not reported within 15 calendar days of the receipt of the reports by the manufacturer.
Appendix 3
Risk 3 (Other) Observations

Adverse Drug Reaction Reporting C.01.016

- The manufacturer has not included in the annual summary reports all domestic serious expected and unexpected adverse drug reactions, non-serious unexpected adverse drug reactions and unusual failure in efficacy reports for new drugs that were received

- The manufacturer has not included in the annual summary reports all foreign serious expected and unexpected adverse drug reactions, and non-serious unexpected adverse drug reactions received

- Follow-up reports to initial case reports were not sought and submitted as information became available

- The manufacturer could not demonstrate that its systems and procedures for the receipt, evaluation and reporting of adverse drug reactions are adequate to effectively sustain adverse drug reaction reporting (1)