

**Our Mandate:**

To manage and deliver a national compliance and enforcement program for blood and donor semen; cells, tissues and organs; drugs (human and veterinary); medical devices and natural health products, collaborating with and across, all regions.

# Health Products and Food Branch Inspectorate

## Inspection Strategy for Good Pharmacovigilance Practices (GVP) for Drugs

**POL-0041**

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**Disclaimer**

*This document does not constitute part of the Food and Drugs Act (Act) or its associated Regulations and in the event of any inconsistency or conflict between that Act or Regulations and this document, the Act or the Regulations take precedence. This document is an administrative document that is intended to facilitate compliance by the regulated party with the Act, the Regulations and the applicable administrative policies.*

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## 1.0 Purpose

This policy describes the Inspectorate program's approach to the planning of Good Pharmacovigilance Practices (GVP) inspections (previously known as Post-Market Reporting Compliance inspections). The purpose of this document is to detail the strategy for the effective and uniform delivery of the GVP inspection program to assess compliance of manufacturers with the *Food and Drugs Act (Act)* and the *Food and Drug Regulations (Regulations)* with regards to reporting adverse drug reactions (ADRs) and reporting unusual failures in efficacy of new drugs to Health Canada.

## 2.0 Background

The *Food and Drug Regulations*, more specifically sections C.01.016 to C.01.020, C.08.007 (h) and C.08.008 (c), set forth regulatory requirements for manufacturers, including but not limited to, the reporting of ADRs and the reporting of unusual failures in efficacy of new drugs to Health Canada. As part of Health Canada's mandate to maximize the safety, quality and efficacy of health products, Health Canada implemented on August 1, 2004, an inspection program for Good Pharmacovigilance Practices (GVP). The GVP inspection program is intended to verify that the manufacturers specifically meets the requirements of sections C.01.016 to C.01.020, C.08.007 (h) and C.08.008 (c) of the *Food and Drug Regulations* pertaining to adverse drug reaction reporting.

## 3.0 Scope

This policy applies to manufacturers as defined in section A.01.010 of the *Food and Drug Regulations*. Within the context of the GVP inspection program, Market Authorization Holders (MAH) and importers are both subject to GVP inspections as their name appears on the label and as such may receive ADRs.

This policy covers the following drugs marketed in Canada for human use which are subject to GVP inspections :

- pharmaceuticals,
- biologics, including biotechnology products, vaccines and fractionated blood products,
- medical gases, and
- radiopharmaceuticals.

This policy does not currently apply to:

- hard surface disinfectants,
- veterinary products,
- natural health products, and
- whole blood and blood components.

## 4.0 Definitions

**Adverse Drug Reaction** - A noxious and unintended response to a drug, which occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of an organic function. ( C.01.001 (1))

**Note:** for new drugs marketed in Canada, reports of unusual failure in efficacy are considered to be a type of adverse drug reactions (ADR) report.

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

**Good Pharmacovigilance Practices (GVP) Regular Inspection** - An inspection during which all of the applicable requirements of the *Food and Drugs Act* and its associated Regulations are assessed.

**Good Pharmacovigilance Practices (GVP) Re-assessment** - A follow-up inspection carried out in situations where the establishment was assigned an overall C rating on a previous inspection but the number or type of observations contained in the previous Inspection Exit Notice are such that corrective action is required within a timely manner. The inspection is focused on, but not restricted, to those sections where deficiencies were observed.

**Good Pharmacovigilance Practices (GVP) Re-inspection** - A follow-up inspection carried out in response to the assignment of a NC rating. The inspection is focused on, but not restricted to, those sections where deficiencies were observed.

**Import** - "To import into Canada a drug for the purpose of sale." (C.01A.001)

**Inspection** - On-site monitoring and assessment against the applicable requirements of the *Food and Drugs Act* and its associated Regulations. Inspections are routinely conducted to assess compliance.

**Inspection Plan** - A detailed strategy outlining critical elements that compliance will be assessed against. The critical elements to be assessed are based on regulatory requirements, recognized, published guidance/standards, aide-memoires and checklists.

**Inspector** - Any person designated as an inspector for the purpose of the enforcement of the *Food and Drugs Act* under subsection 22(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 (A.01.010) Within the context of the GVP inspection program, MAH and importers are subject to GVP inspections as their name appears on the label and as such, may receive ADRs.

**Market Authorization Holder** - For the purpose of this document means the entity that holds the Notice of Compliance or the Drug Identification Number (DIN).

**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; (b) a drug that is a combination of two or more drugs, with or without other ingredients, and that has not been sold in that combination or in the proportion in which those drugs are combined in that drug, for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that combination and proportion for use as a drug; or (c) a drug, with respect to which the manufacturer prescribes, recommends, proposes or claims a use as a drug, or a condition of use as a drug, including dosage, route of administration, or duration of action and that has not been sold for that use or condition of use in Canada, for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that use or condition of use of that drug." (C.08.001)

Generally, if a notice of compliance (NOC) was issued for a drug, then that drug is considered to be a "new drug", regardless of how long it has been on the market.

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

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

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

**Unusual Failure in Efficacy** - This has been considered an adverse drug reaction for many years under the *Food and Drug Regulations*. It applies to new drugs only. The underlying principle is that if a health product fails to produce the expected intended effect, there may be an adverse outcome for the patient, including an exacerbation of the condition

for which the health product is being used. Clinical judgment should be exercised by a qualified health care professional from the market authorization holder (MAH) to determine if the problem reported is related to the product itself, rather than one of treatment selection or disease progression since health products cannot be expected to be effective in 100% of the patients. One example of unusual failure in efficacy is a previously well-stabilized condition that deteriorates when the patient changes to a different brand or receives a new prescription. Another example of a case that should be reported on an expedited basis is a life-threatening infection where the failure in efficacy seems to be due to the development of a newly resistant strain of bacterium previously regarded as susceptible.

For additional definitions, consult the documents listed in Section 8.0 Associated Documents

## 5.0 Compliance Activities

Any manufacturers marketing drugs in Canada must comply with Divisions 1 and 8 of the *Food and Drug Regulations*, including the adverse drug reaction reporting and reporting of failure in efficacy of new drug drugs. The Inspectorate program provides information and promotes voluntary compliance with Canadian regulatory requirements. Compliance is assessed by conducting inspections with a different cycle frequencies of these establishments based on a priority ranking scale and a risk-based approach.

### 5.1 Inspections

Within the scope of the GVP Drug Inspection program, manufacturers of pharmaceutical, biological and radiopharmaceutical drugs are inspected by the Inspectorate program and are assessed for compliance with the *Regulations* pertaining to the reporting of adverse drug reactions, specifically sections C.01.016 to C.01.020 of the *Regulations*, and for reporting failure in efficacy of new drugs, as set forth in sections C.08.007 (h) and C.08.008 (c) of the *Regulations*.

#### 5.1.1 Selection of Sites for Inspection

The Inspectorate program is responsible for site selection. The guiding principle in the selection process is the safety and efficacy of drugs marketed in Canada. The criteria listed below may be considered, but, ultimately, Health Canada must mitigate the greater risk to health. The selection of establishment subject to GVP inspection will be based on a variety of criteria including, but not limited to:

- Compliance of the establishment (facility):
  - Date of last inspection
  - Rating of previous GVP inspections and type of observations that were noted
- Information on the drug products:
  - Therapeutic Class
- Adverse drug reactions:
  - Lateness based on the 15-day regulatory reporting period
  - Type of ADR reports that were reported late

**Note :** The choice of establishment to be inspected is reviewed periodically in consultation with the Therapeutic Products Directorate (TPD), the Biologics and Genetic Therapies Directorate (BGTD) and the Marketed Health Products Directorate (MHPD) of the Health Products and Food Branch (HPFB).

### 5.1.2 Inspection activities

An inspector of the Inspectorate program will contact the establishment to schedule a GVP inspection. Notice of an upcoming GVP inspection may or may not be provided, however inspections are generally announced as a courtesy. Any changes to the scheduled date of inspection may be approved, but will be at the discretion of the Inspectorate Program and will have to be adequately justified.

The duration of the inspection will vary depending on the type of activities, the size of the establishment, and the volume of ADRs recorded.

**Note :** A re-inspection or a re-assessment for Good Pharmacovigilance Practices may be required as a follow-up.

### 5.2 Inspection Rating and Reporting

A GVP inspection will result in one of the two following ratings:

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

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

All GVP observations are based on the Health Canada guidance entitled [Good Pharmacovigilance Practices \(GVP\) Guidelines \(GUI-0102\)](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0102_gvp-eng.php) ([http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0102\\_gvp-eng.php](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0102_gvp-eng.php)) and a risk level is assigned to each observation according to the Health Canada guidance entitled [Risk Classification of Good Pharmacovigilance Practices \(GVP\) Observations \(GUI-0063\)](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0063_gvp-eng.php) ([http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0063\\_gvp-eng.php](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0063_gvp-eng.php)). All observations are discussed with the firm during the exit meeting and confirmed to the establishment in the Inspection Exit Notice. Either a C rating or NC rating is assigned at the conclusion of the inspection.

### 5.3 Enforcement Actions

During the course of an inspection, an inspector may face situations of non compliance. These situations will be assessed according to Health Canada's risk determination principles and appropriate enforcement actions will be taken in accordance with the principles described in [Compliance and Enforcement Policy \(POL-0001\)](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/pol/pol_1_tc-tm-eng.php) ([http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/pol/pol\\_1\\_tc-tm-eng.php](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/pol/pol_1_tc-tm-eng.php)).

## 6.0 Responsibilities

Compliance is assessed through inspections, compliance verifications, and investigations conducted by inspectors of the Inspectorate program designated under Section 22 (1) of the *Food and Drugs Act*. Inspections for compliance with the *Food and Drugs Act* and its Regulations are conducted under the authority of Section 23 of the *Food and Drugs Act*, with reference to relevant policies and guidance documents.

It is the responsibility of the Inspectorate Program and the Marketed Health Products Directorate (MHPD) to collaborate and act in partnership in the application of this Inspection Strategy. It is the Inspectorate program's responsibility to perform inspections and the responsibility of MHPD to analyze the data provided by the Inspectorate program in conjunction with their objectives.

## 7.0 Effective Date

This Policy will become effective February 11, 2013.

## 8.0 Associated Documents

1. [Food and Drugs Act and Food and Drug Regulations, Department of Justice Canada](http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/index.html)  
([http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,\\_c.\\_870/index.html](http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/index.html))
2. [Compliance and Enforcement Policy \(POL-0001\), Version 2, Health Canada, May 2005](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/pol/pol_1_tc-tm-eng.php)  
([http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/pol/pol\\_1\\_tc-tm-eng.php](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/pol/pol_1_tc-tm-eng.php))
3. [Guidance Document for Industry – Reporting Adverse Reactions to Marketed Health Products \(2011\)](http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2011-guidance-directrice_reporting-notification/index-eng.php)  
([http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/\\_guide/2011-guidance-directrice\\_reporting-notification/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2011-guidance-directrice_reporting-notification/index-eng.php))
4. [Good Pharmacovigilance Practices \(GVP\) Guidelines \(GUI-0102\)](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0102_gvp-eng.php)  
([http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0102\\_gvp-eng.php](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0102_gvp-eng.php))
5. [Risk Classification for Good Pharmacovigilance Practices \(GVP\) Observations \(GUI-0063\)](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0063_gvp-eng.php)  
([http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0063\\_gvp-eng.php](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0063_gvp-eng.php))