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

Summary report of the Drug Good Manufacturing Practices (GMP) Inspection Program
April 1, 2006 to March 31, 2011

Supersedes:
New Document

Date issued:
December 21 2012

Date of implementation:
December 21, 2012

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.
# Table of Contents

1.0 Background .......................................................................................................................... 3

1.1 Inspections .......................................................................................................................... 3

2.0 Overview of Domestic Human and Veterinary Drug Good Manufacturing Practices (GMP) Program .................................................. 4

2.1 Profile of Industry over last 5 years ...................................................................................... 4

2.1.1 National Distribution of Licensed Establishments by Activity (April 2011) ....................... 4

2.1.2 Number of Inspections performed Nationally by Activity ................................................ 5

2.1.3 C/NC Ratings Per Year .................................................................................................... 5

2.2 Risk Ratings ........................................................................................................................ 6

2.2.1 : Table Overall Risk/Observation Results ..................................................................... 6

2.2.2 : Sections of the Food and Drug Regulations Against which Risk 1 Observations were cited .............................................................................................................. 6

2.2.3 : Regulations Most Frequently Cited ............................................................................... 7

2.2.4 : Most Common Observations Cited ............................................................................... 8

3.0 Appendices ........................................................................................................................... 9

3.1 Definitions .......................................................................................................................... 9

3.2 Quality Documents – Policies and Guidelines ..................................................................... 9
1.0 Background

The mandate of the Health Products and Food Branch (HPFB) of Health Canada is to take an integrated approach to the management of the risks and benefits of health products and food by minimizing the potential hazards they may present to Canadians while maximizing the safety of these products. Canadians can be empowered to make informed decisions that are beneficial to their health, through the implementation of regulatory systems and providing reliable information regarding health products and food.

The HPFB Inspectorate has the role of delivering a national compliance and enforcement program for all products under the mandate of the HPFB, with the exception of food products. The regional offices located in British Columbia, Alberta, Manitoba and Saskatchewan, Ontario, Quebec, and Atlantic Canada, along with laboratories in Toronto and Longueuil ensure that the Inspectorate has a national reach. The authority to deliver this compliance and enforcement program for these products is derived from the Food and Drugs Act and its Regulations. The Inspectorate’s 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) provides the guiding principles for the fair, consistent and uniform application and enforcement of the Food and Drugs Act and its Regulations.

Good Manufacturing Practices (GMP) are the part of quality assurance that helps to ensure that drugs are consistently produced and controlled to meet the quality standards appropriate to their intended use, as required by their marketing authorizations. The Drug GMP Compliance program is part of the Health Products and Food Branch Inspectorate (Inspectorate), and is responsible for conducting inspections of establishments that are involved in activities covered by the Establishment Licensing framework. These inspections are conducted to verify the compliance with GMPs (Part C, Division 2 of the Food and Drugs Regulations) which is a requirement for the issuance of an Establishment Licence. To ensure a uniform application of these requirements and to help the industry to comply, the Inspectorate has developed the Good Manufacturing Practices(GMP) Guidelines – 2009 Edition, Version 2 (GUI-0001-Eng) (http://web.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php) as well as a series of guides and other related documents, references to which can be found in Section 3.2 of this document.

1.1 Inspections

Inspections are conducted to assess compliance with Division 2 of Part C of the Food and Drug Regulations. In order to conduct activities relating to the fabrication, packaging/labelling, testing, importation, distribution or wholesaling of a category of drugs listed in Table II of Section C.01A.008 of the Food and Drug Regulations, an establishment must comply with the requirements of Division 2 of the Food and Drug Regulations, which covers GMPs. As evidence of this compliance, an Establishment Licence is issued. Division 1A of Part C of the Food and Drug Regulations outlines the requirements for Establishment Licences.

The initial inspection of an establishment conducting licensable activities is triggered by the receipt of a Drug Establishment Licence Application. Establishments are advised to submit their application once they are ready to begin licensable activities for any product subject to Division 1A of the Food and Drug Regulations or once they have received drug marketing authorization. A Pre-Application Package has been created to provide guidance on the elements and systems that must be in place in order for an establishment to be considered ready for their initial inspection. This Package can be found on the Health Canada website and is referenced in section 3.2 of this document. The Drug Establishment Licence Application and Instructions can also be found on Health Canada’s website – Establishment Licences (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/ licences/index-eng.php).

The Inspectorate endeavours to perform an initial on-site inspection within 3 months of the date of the receipt of a complete Drug Establishment Licence Application by the Establishment Licensing Unit (ELU). A regular inspection is generally conducted within 12 months of the initial inspection. The date of the next inspection depends on the activities being conducted by the establishment being inspected. Fabricators, Packagers/Labelers and Testing Labs are inspected on a two year cycle. Importers, Wholesalers and Distributors are inspected on a three year cycle. If an establishment is conducting multiple activities concurrently, the higher risk activity dictates the inspection cycle. More detailed information can be found in the document GMP Inspection Policy for Canadian Drug Establishments (POL-0011) (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/pol/pol_0011_tc-tm-eng.php).
Establishments are encouraged to ensure that all of the applicable systems are in place prior to applying for an Establishment Licence. It is recommended that an establishment refer to Good Manufacturing Practices (GMP) Guidelines – 2009 Edition, Version 2 (GUI-0001) (http://web.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php), applicable GMP Annexes and the Guidance on Drug Establishment Licences and Drug Establishment Licensing Fees (GUI-0002) (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/licences/directives/gui-0002-eng.php) for further information. If, following an assessment of a Drug Establishment Licence Application, Health Canada determines that a site is not ready for an inspection the Licence Application will be refused.

The scope of the inspection depends not only on the licensable activities being assessed, but also the category and dosage form class of products involved. During an inspection, the inspector will record all deviations to Division 2 of Part C of the Food and Drug Regulations as observations. Where possible, the establishment will be given the opportunity to correct observations as they are made during an inspection, however immediate action will be taken if a risk to health is identified. Following the inspection, the establishment will be expected to submit a corrective action plan to address the observations noted. A defined timeframe for the submission of the establishment's response may be imposed and may vary according to the severity of the observations noted in the report.

If the establishment is deemed to be compliant, it is given a C rating (Compliant). NC (Non compliant) ratings are issued to establishments who are deemed to be non-compliant with the GMP regulations. An NC rating may have serious consequences for a company, ranging from the implementation of important corrective measures to the temporary suspension or termination of the Establishment License.

2.0 Overview of Domestic Human and Veterinary Drug Good Manufacturing Practices (GMP) Program

2.1 Profile of Industry over last 5 years

2.1.1 National Distribution of Licensed Establishments by Activity (April 2011)

![Figure 2.1.1 Snapshot of the National Distribution of Licensed Establishments by Activity in April 2011. As one establishment may be licensed for multiple activities the total number of actual establishments nationally would not be equal to the total number of licence holders for each of the activities depicted in this Figure.](image-url)
2.1.2 Number of Inspections performed Nationally by Activity

![Graph showing number of inspections by activity from 2006 to 2010]

**Figure 2.1.2** Number of inspections nationally by activity performed over the past five fiscal years (FY 2006-07 – FY 2010-11). Data was calculated by activity thus Establishments conducting more than one activity would be counted more than once, therefore the total number of establishments inspected cannot be inferred from this chart.

2.1.3 C/NC Ratings Per Year

![Graph showing C/NC ratings over five fiscal years]

**Figure 2.1.3** Rating results of Inspections conducted nationally over the past 5 fiscal years (FY 2006-07 – FY 2010-11). Canadian industry is highly compliant and with less than 6 % found to be non compliant in the 2010-2011 fiscal year.
2.2 Risk Ratings

2.2.1 Table Overall Risk/Observation Results

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>Total Number of Inspections Conducted</th>
<th>Total Observations in each Risk Category (Percentage)</th>
</tr>
</thead>
</table>
| 2006-2007   | 303                                  | Risk 1: 0.2%  
Risk 2: 59%  
Risk 3: 41% |
| 2007-2008   | 383                                  | Risk 1: 0.2%  
Risk 2: 57%  
Risk 3: 42% |
| 2008-2009   | 447                                  | Risk 1: 0.3%  
Risk 2: 57%  
Risk 3: 42% |
| 2009-2010   | 393                                  | Risk 1: 0.9%  
Risk 2: 54%  
Risk 3: 45% |
| 2010-2011   | 440                                  | Risk 1: 0.9%  
Risk 2: 54%  
Risk 3: 45% |

Table 2.2.1 Overall Risk ratings of Observations noted during inspections. There is a relative stability in total number of observations per year and the percentage of Risk two ratings is consistently the highest of the three Risk levels from year to year.

2.2.2 Sections of the Food and Drug Regulations against which Risk 1 observations were cited by Fiscal Year (April 1, 2006 - March 31, 2011).

Figure 2.2.2 Sections of the Food and Drug Regulations against which Risk 1 observations were cited by Fiscal Year (April 1, 2006 - March 31, 2011).
The spike in the number of Risk 1 observations recorded in 2009 is attributed to the implementation of the new version of GUI-0001 Good Manufacturing Practices (GMP) Guidelines, which came into force in 2009. This document provided specific guidance for inspections with respect to the requirements surrounding sterile products and it is assumed to have resulted in the increase in Risk 1 observations recorded by Inspectors against Quality Control and Sterile Products sections of the FDR as denoted in the graph.

A draft outlining the proposed changes to GUI-0001 was posted for comment preceding the implementation in 2009, giving Industry advanced notice of the Inspectorate's expectations as part of compliance promotion activities. It should be noted that as a result of the issuance of this guidance, the number of observations against these two sections of the FDR decreased in 2010 onwards.

### 2.2.3 : Regulations Most Frequently Cited

![Bar chart showing the percentage of total observations by fiscal year (2006-2010) for different regulatory sections.]

Figure 2.2.3 : Regulations most commonly cited by fiscal year (2006-2010) C.02.015 Quality Control Department consistently sees the highest number of observations.
2.2.4 Most Common Observations Cited
The three regulations against which the majority of observations are cited are C.02.011 (Manufacturing Control), C.02.012 (Manufacturing Control) and C.02.015 (Quality Control Department). Examples of common observations cited for each of these regulations are as follows:

<table>
<thead>
<tr>
<th>Regulation</th>
<th>Example of observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.02.011, Manufacturing Control</td>
<td>- Process Validation for critical production processes not conducted or incomplete</td>
</tr>
<tr>
<td></td>
<td>- Incomplete manufacturing procedures / batch documents; failure to follow manufacturing</td>
</tr>
<tr>
<td></td>
<td>procedures</td>
</tr>
<tr>
<td></td>
<td>- Incomplete Packaging Documents or Procedures</td>
</tr>
<tr>
<td>C.02.012, Manufacturing Control</td>
<td>- Inadequate/Lack of Quality Agreements</td>
</tr>
<tr>
<td></td>
<td>- Inadequate/Lack of Recall system/procedure</td>
</tr>
<tr>
<td></td>
<td>- Absence of/ inadequate Self Inspection Program</td>
</tr>
<tr>
<td>C.02.015 Quality Control Department</td>
<td>- Inappropriate procedures for handling storage and shipment of drug products with</td>
</tr>
<tr>
<td></td>
<td>respect to temperature requirements</td>
</tr>
<tr>
<td></td>
<td>- Laboratory Operations issues</td>
</tr>
</tbody>
</table>

Table 2.2.4 Most Common Observations Cited
3.0 Appendices

3.1 Definitions

**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.

**Inspection**: On-site monitoring and assessment against the applicable requirements of the Food and Drugs Act (FDA) and its associated Regulations. Inspections are routinely conducted on a predetermined cycle or as required to assess compliance.

**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.

**Observation**: A deviation or deficiency to GMPs 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 1 for “critical” to 2 for “major” to 3 for “other”.

- **Critical observation (Risk 1)**: Observation describing a situation that is likely to result in a non-compliant product or a situation that may result in an immediate or latent health risk and any observation that involves fraud, misrepresentation or falsification of products or data.
- **Major observation (Risk 2)**: Observation that may result in the production of a drug not consistently meeting its marketing authorization. Certain Risk 2 observations may be upgraded to Risk 1.
- **Other observation (Risk 3)**: Observation that is neither critical nor major but is a departure from the GMP.

**Regular Inspection**: An inspection during which all of the applicable requirements of the FDA and its associated Regulations are assessed.

3.2 Quality Documents – Policies and Guidelines

GMP related quality documents are available on Health Canada’s Web site in the Compliance and Enforcement (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/index-eng.php) section. For more information on the GMP Inspection Program, you are invited to consult the following documents in particular:

- [Compliance and Enforcement Policy (POL-0001)](http://hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/pol/pol_1_tc-tm_e.html)