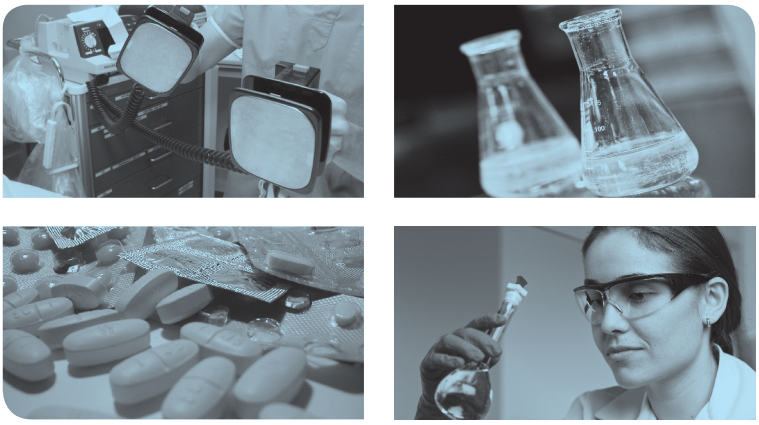
# INSPECTORATE PROGRAM



# ANNUAL INSPECTION SUMMARY REPORT 2012 – 2013

Canada


HEALTH · SANTÉ
CANADA
INSPECTOR
INSPECTEUR

# OUR VISION

To be a trusted national organization committed to regulatory compliance and enforcement activities of health products based on modern, risk management decision-making strategies that will effectively contribute to the safety of health products and positively impact the health of Canadians.

# OUR MISSION

The primary role of the Inspectorate Program is to deliver a national compliance and enforcement program for health products under the mandate of the Health Products and Food Branch (HPFB), in collaboration with the Regions and Programs Bureau (RAPB).

# MESSAGE FROM THE DIRECTORS GENERAL

## Welcome to the Health Canada Inspectorate Program Annual Inspection Summary Report for 2012 – 2013.

The Inspectorate Program is pleased to share with you its first consolidated annual inspection summary report. This report reflects our commitment to transparency by making compliance information readily available to Canadians.

The Inspectorate Program is responsible for monitoring continued compliance of health products authorized for sale in Canada, with the *Food and Drugs Act* and its associated Regulations. This particular report outlines inspection activities conducted by the Inspectorate for the fiscal year 2012–2013. The inspection results are summarized by product line and inspection type, and are explained according to the relevant regulatory requirement(s). In total, Health Canada conducted 1,257 inspections, made hundreds of observations requiring corrective actions, and issued 37 non-compliant ("NC") ratings.

In the coming years, we will continue to seek innovative ways of delivering the National Inspection Programs. We are proud of the professionalism and expertise of the Inspectorate team across the country, and we are confident that by working with our partners we can pursue positive outcomes in support of Health Canada's mandate to improve the health and safety of Canadians.

We hope that you find this material useful and informative.

Robin Chiponski
Director General
Health Products and Food Branch Inspectorate

Marie-France Bérard
Regional Director General, Quebec Region
Executive File Lead, Inspectorate Program
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# EXECUTIVE SUMMARY

**The primary role of Health Canada's Inspectorate Program is to deliver a national compliance monitoring and enforcement program as it relates to health products, including drugs (human and veterinary), medical devices, natural health products, blood, donor semen, and cells, tissues and organs.**

This mandate is achieved through a number of core activities such as: inspections, complaint follow-up (incidents, recalls, public advisories, compliance verifications and investigations), border integrity activities, and laboratory analysis. The program is designed to assess and monitor risks associated with non-compliance with the *Food and Drugs Act* and its associated Regulations. The Inspectorate Program delivers this through the Health Products and Food Branch (HPFB) Inspectorate and the Regions and Programs Bureau (RAPB).

The Inspectorate has several inspection streams with different regulatory requirements based on the product types listed below:

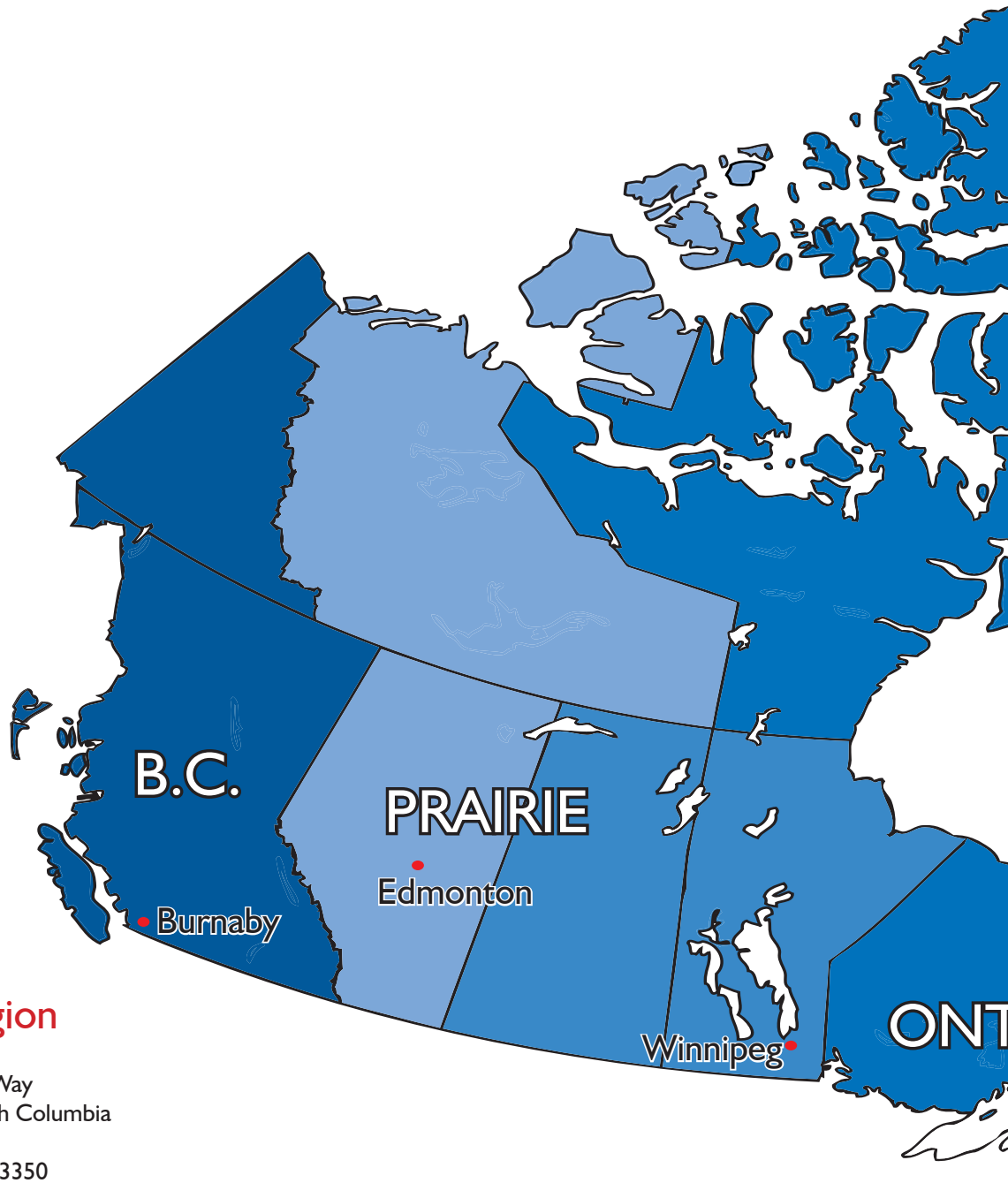
- Blood
- Cells, Tissues and Organs for transplantation
- Drug Good Clinical Practices (GCP )
- Drug Good Manufacturing Practices (GMP)
- Drug Good Pharmacovigilance Practices (GVP)
- Medical Devices
- Semen for assisted conception

Once licensed or registered, domestic establishments are inspected to monitor continued compliance on a predetermined, risk-based schedule. Between April 2012 and March 2013, the Inspectorate conducted 1,257 on-site inspections in Canada. The Inspectorate also assesses the compliance of foreign drug manufacturing sites from where products are imported into Canada. Only manufacturers meeting GMP requirements are included in the foreign site annex to the licence. Prior to licensing, all observations listed in the inspection report must be addressed and brought to a satisfactory level of compliance by the manufacturers.

In this report, inspection results from April 2012 to March 2013 are summarized by product and inspection type, and explained according to the relevant regulatory requirement(s). Inspection findings indicate a departure from regulatory requirements and are classified as "critical", "major" and "others", depending on the risk of producing a product which is or could be harmful. The Inspectorate issued non-compliant ("NC") ratings to 37 establishments. An inspection for assessment of compliance may result in deficiencies being identified that require the implementation of corrective measures by the company.

A "NC" rating may result in the suspension of an establishment license, and if the deficiencies are left unresolved, may lead to the cancellation of the licence. The potential impact of deficiencies on the quality of products may result in a recall of products already distributed, in addition to advisories issued to notify Canadians of any potential risks to health or disruption of supply of approved products.

The Inspectorate plays a key role in maintaining the quality of health products in the Canadian marketplace. Regulated parties are responsible for complying with the *Food and Drugs Act* and its associated Regulations. When non-compliance is identified, Health Canada takes appropriate compliance and enforcement actions. Health Canada is committed to making compliance information available to Canadians as a way of demonstrating the effectiveness of the inspection programs, and revealing how well regulated parties are complying with the regulations. This report contributes to the transparency initiative by providing information to Canadians that will help maintain confidence in the safety and quality of health products in Canada.

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# CHAPTER 1

# BLOOD INSPECTION PROGRAM

## BACKGROUND

In Canada, human blood and blood components intended for transfusion or further manufacturing into human drugs are regulated under the *Food and Drugs Act* (Act) and the *Food and Drug Regulations* (Regulations), specifically Part C, Division 1A, 2, and 4.

The purpose of the Regulations is to minimize potential health risks to Canadians by setting out safety, quality and efficacy requirements. As per Part C, Division 1A of the Regulations, blood operators are required to obtain an establishment licence and market authorization to perform any of the six licensable activities that include: fabricate, test, package/label, distribute, wholesale and import.

In fiscal year 2012–2013, there were 3 blood operators with 58 buildings/sites across Canada. Every building/site in which a blood operator proposes to conduct licensable activities is required to be licenced under its establishment's licence.

The frequency with which blood inspections are conducted is outlined in the *Inspection Strategy for Blood and Source Plasma Establishments* (POL-0039). The main objective of an inspection is to assess blood operators' compliance with the Regulations to help ensure that blood and blood components are consistently distributed and controlled to meet the quality standards appropriate to their intended use, as required by their marketing authorizations.

## WHAT'S NEW?

Health Canada has consolidated existing requirements into regulations specific for human blood and blood components which apply the level of oversight that is commensurate with the level of risk of the activities performed by each establishment. The *Blood Regulations* were published in *Canada Gazette II* and will come into force in October 2014.

## INSPECTION RESULTS AND STATISTICS

### INSPECTION STATISTICS

During the period covered in this report, a total of 33 inspections were conducted and all establishments were found to be in compliance with the Regulations.

It is important to note that a compliant rating does not mean that there are no observations or corrective actions required. A total of 193 observations were noted and risk rated. Each observation may have included a number of similar deficiencies. The majority of these observations were assigned a Risk 3 (87%) and the remaining was assigned Risk 2 (13%). Risk 1 observations were not noted.

Following the inspections, blood operators' corrective actions were assessed and found to be acceptable. Therefore, a compliant rating was assigned for all inspected buildings/sites.

## MOST COMMON OBSERVATIONS CITED

Figure 1.1 illustrates the prevalence of observations associated with the different sections of the Regulations. The majority of observations were cited against Manufacturing Control C.02.011, Equipment C.02.005 and Records C.02.020, followed by Personnel C.02.006, Premises C.02.004 and Raw Material Testing C02.009.

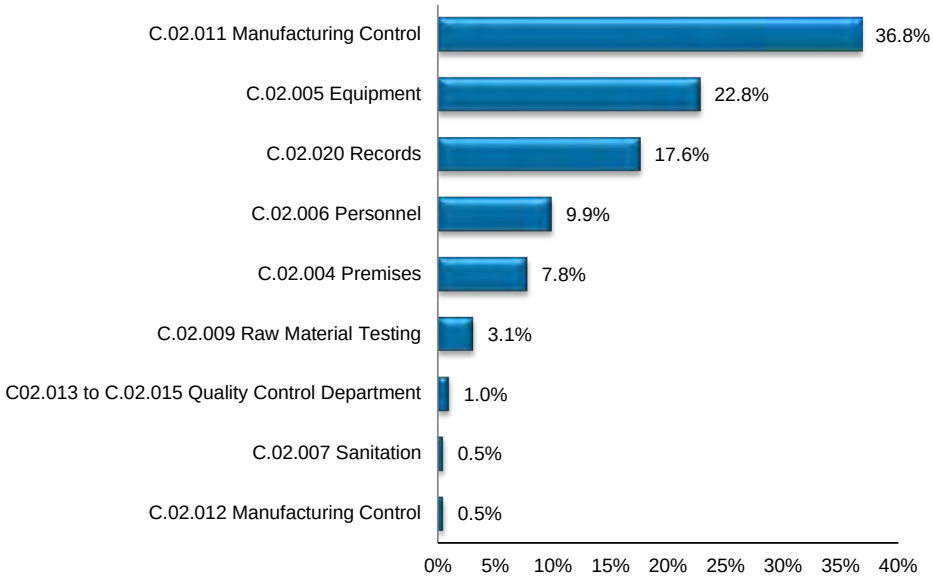


***Figure 1.1*** Sections of the *Food and Drug Regulations* most commonly cited as a percentage of the total number of observations cited during inspections conducted nationally. (Fiscal Year: April 1, 2012 – March 31, 2013)

Inspections are conducted by inspectors in regional offices across Canada. During an inspection, the inspector notes all deviations cited against the Regulations as observations and each observation is risk assigned as critical (Risk 1), major (Risk 2), or minor (Risk 3) as per the principles and guidelines set forth in the *Risk Classification of Observations made during Inspections of Blood Establishments* (GUI-0061).

Depending on the severity of the observations, i.e. number and types of occurrences, an overall rating of compliant ("C") or non-compliant ("NC") is issued and corrective measures are required for each observation. A "NC" rating has serious consequences for an establishment, ranging from the implementation of immediate corrective measures to the suspension and/or cancellation of the establishment's licence.

## RISK RATINGS OF OBSERVATIONS

During the 33 regular inspections a total of 193 observations were noted. The majority of these observations were of Risk 3 (87%) and the remaining were of Risk 2 (13%). There were no Risk 1 observations.

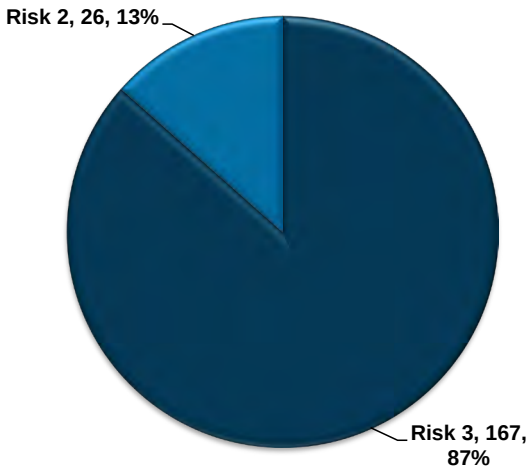


***Figure 1.2*** Distribution of risk ratings of observations during inspections conducted nationally. (Fiscal Year: April 1, 2012 – March 31, 2013)

## TABLE 1.1- EXAMPLES OF RISK 2 OBSERVATIONS CITED

| *Food and Drug Regulations* | Example of Risk 2 Observations |
|---|---|
| Manufacturing Control C.02.011 | The establishment did not demonstrate adequate oversight for the temperature monitoring activities performed by a third party. For example, there was no written agreement between the establishment and the vendor providing temperature monitoring of the blood bank. Some documentation was provided, such as an escalation contact list and a zone alarm list for the site. |
| Equipment C.02.005 | The establishment was unable to demonstrate adequate control of the critical equipment in some cases. Specifically, the establishment does not maintain a critical equipment list for the department (including mobile and fixed sites) and there is no process to ensure that equipment that missed preventative maintenance remains on the schedule in subsequent months and/or taken out of service. The equipment located at the mobile clinic had preventative maintenance that was not performed as scheduled. |
| Personnel C.02.006 | There is no process in place to ensure training matrices are current or up to date and reflect the actual training requirements. For example:<br>i. Various training documents were not listed for QC Tech on the Quality Control training matrices. It was confirmed during the inspection that this was required training.<br>ii. Various training documents were not listed as a requirement for a Senior Tech on the Component Production training matrix. However, the Senior Tech was trained on these documents. It was confirmed during the inspection that this was required training.<br>iii. Various training documents were listed as "N/A" for the position of Building Technician on the Facilities training matrix. It was confirmed during the inspection that this was required training. |

## TABLE 1.2 - EXAMPLES OF RISK 3 OBSERVATIONS CITED

| *Food and Drug Regulations* | Example of Risk 3 Observations |
|---|---|
| Manufacturing Control<br>C.02.011 | During the review of records for Donor Testing, the following was observed:<br>a. The history review logs did not record the times, contrary to standard operating procedures.<br>b. The test logs stated "NAT" in section 1 rather than a pager/ cellphone number. |
| Equipment<br>C.02.005 | The equipment preventative maintenance sticker indicated that the preventative maintenance was completed. However, the verification log indicated that the preventative maintenance was completed on a different date. |
| Records<br>C.02.020 | During record review, the following were noted:<br>a. On several occasions the completed form was missing the "completed by" initials, yet the blood order had been completed and distributed.<br>b. The documents confirming receipt of products had been stamped with the required stamp, but the shipment assessment boxes had not been checked to indicate assessment of the shipment which is contrary to standard operating procedures.<br>c. The volume monitoring chart had the average volume of the first five runs marked as 51 on the chart, yet the actual average as per the volume log was 49.<br>d. The test record was missing the selection of Pass or Fail; however the result was a Pass and had been input correctly to the database. |

# CHAPTER 2

# CELLS, TISSUES AND ORGANS (CTO) INSPECTION PROGRAM

## BACKGROUND

In Canada, organs and minimally manipulated cells and tissues are regulated under the *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* (CTO Regulations). The purpose of the CTO Regulations is to minimize the potential health risks to recipients of human cells, tissues and organs for transplantation.

The CTO Regulations address safety in the processing and handling of these products, resulting in improved protection of the health and safety of transplant recipients in Canada. As per the CTO Regulations, source establishments, establishments that distribute within Canada, and establishments that import for further distribution are required to register with Health Canada, and provide an attestation that they are in compliance with the CTO Regulations.

The frequency with which CTO inspections are conducted is outlined in the *Inspection Strategy for Cells, Tissues and Organs Establishments* (POL-0057). The main objective of an inspection is to assess compliance with the CTO Regulations.

During the period covered in this report, a total of 41 out of 136 registered Canadian CTO programs were inspected and were found to be in compliance with the CTO Regulations.

## WHAT'S NEW?

Since April 2012, the following documents relating to cells, tissues and organs were published on Health Canada's website: *Guidance on Classification of Observations for Inspection of Cells, Tissues, and Organs Establishments* (GUI-0101), *Inspection Strategy for Cells, Tissues and Organs Establishments* (POL-0057), and *Summary Report of Inspections of Cells, Tissues and Organs Establishments Conducted from August 2009 to June 2012*.

In addition, in September 2012, Health Canada consulted on a revised Draft 2nd Edition *Guidance Document for Cell, Tissue and Organ Establishments: Safety of Human Cells, Tissues and Organs for Transplantation* (CTO Guidance Document). The purpose of the CTO Guidance Document is to provide further clarification and interpretation of the CTO regulatory requirements.

# INSPECTION RESULTS AND STATISTICS

## STATISTICS ON REGISTERED ESTABLISHMENTS

As of March 2013, a total of 106 Canadian CTO establishments are registered with Health Canada. It is important to note that some establishments have opted to register each of their individual programs (for example, kidney program, liver program, lung program, tissue bank) as a separate entity and, therefore, the total number of registered Canadian CTO programs is not equal to the total number of registered CTO establishments.

For the purpose of this summary report, and consistency in statistical analysis and reporting, all data presented in this report is based on 136 registered Canadian CTO programs.

Figure 2.1 shows the distribution of the 10 types of domestic CTO programs that have registered with Health Canada.

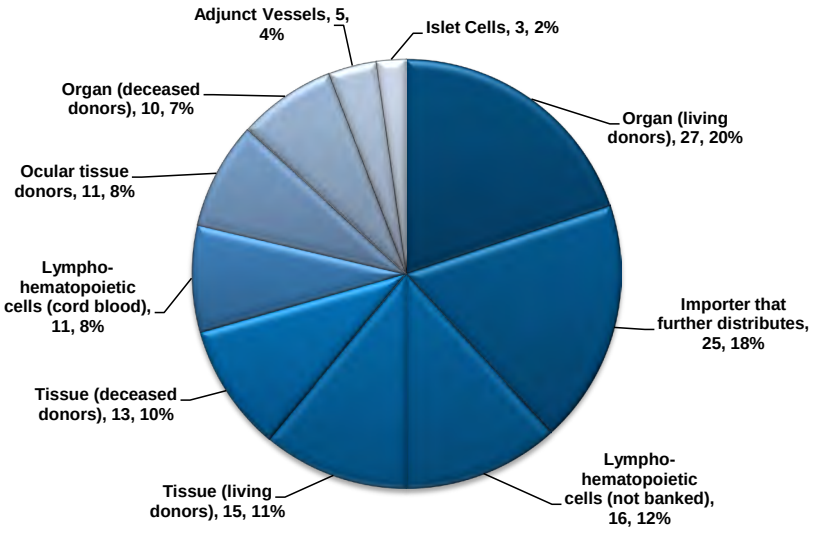


***Figure 2.1*** National distribution of the ten types of registered Canadian CTO programs. (Fiscal Year: April 1, 2012 – March 31, 2013)

## INSPECTION STATISTICS

Within the period covered in this report, a total of 41 regular inspections were conducted. All CTO programs inspected were found to be overall compliant with the CTO Regulations.

Inspections are conducted by inspectors in regional offices across Canada. During an inspection, the inspector records all deviations cited against the CTO Regulations as observations.

Prior to finalising any observations, they are peer reviewed for uniformity and each observation is classified individually as critical (Risk 1), major (Risk 2), or minor (Risk 3).

All ratings are assigned in accordance with the principles and guidelines set forth in the *Guidance on Classification of Observations for Inspection of Cells, Tissues, and Organs Establishments* (GUI-0101).

## MOST COMMON OBSERVATIONS CITED

Figure 2.2 illustrates the prevalence of observations associated with the different sections of the CTO Regulations. The observations were grouped in accordance with the CTO regulatory requirements. The majority of observations were cited against requirements for quality assurance system (sections 70 – 76), records (sections 55 – 63), personnel, facilities, equipment and supplies (sections 64 – 69), donor suitability assessment (sections 18 – 23), and packaging and labelling (sections 28 – 33).

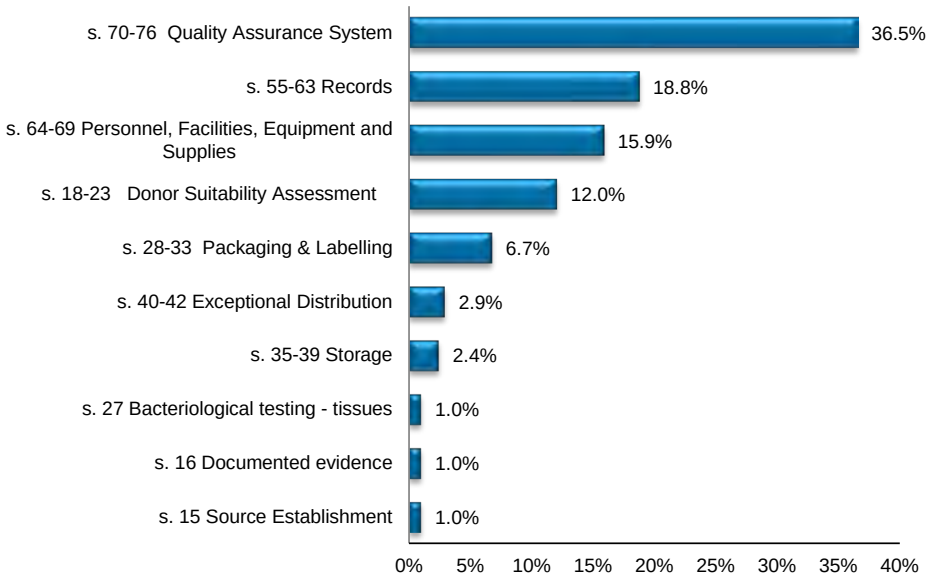


***Figure 2.2*** The top ten sections of the *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* (CTO Regulations) most commonly cited as a percentage of the total number of observations cited during inspections conducted nationally. (Fiscal Year: April 1, 2012 – March 31, 2013)

Depending on the severity of the observations–for example, number and types of occurrences of risk observation–an overall rating of compliant ("C") or non-compliant ("NC") is issued and corrective measures are required for each risk observation.

It is important to note that a compliant rating does not mean that there are no observations or corrective actions required. A "NC" rating has serious consequences for a program, ranging from the implementation of immediate corrective measures to the cancellation of the CTO registration number.

In addition to the regular inspections, Health Canada also conducted four re-inspections of programs that were rated non-compliant in 2011–2012. The re-inspections focused on, but were not restricted to, those sections of the CTO Regulations where violations were observed during the regular inspection.

The results of the four re-inspections indicated that the implicated programs successfully implemented appropriate corrective measures and hence were found to be in compliance with the CTO Regulations.

## RISK RATINGS OF OBSERVATIONS

During the 41 regular inspections, a total of 208 observations were noted. The majority of these observations were of Risk 3 (85%) and the remaining were of Risk 2 (15%). There were no Risk 1 observations.

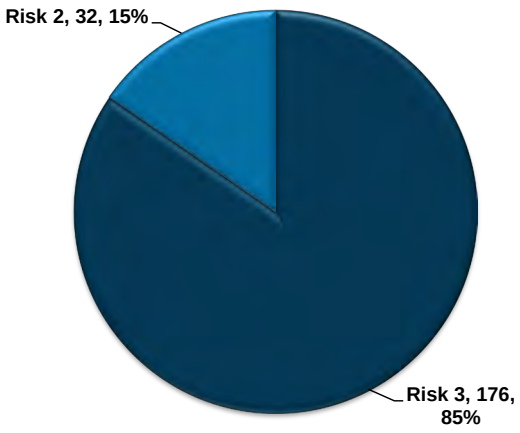


***Figure 2.3*** Distribution of risk ratings of observations during inspections conducted nationally. (Fiscal Year: April 1, 2012 – March 31, 2013)

## TABLE 2.1 - EXAMPLES OF COMMON OBSERVATIONS CITED

| *CTO Regulations* | Example of Observations |
|---|---|
| Section 70-76 Quality Assurance System | • Although there was a mechanism implemented in October 2009 to verify that each order of tissues has been determined safe for transplantation by the source establishment, this mechanism was not described in a procedure and was not followed systematically.<br>• SOP does not define who is responsible to review donor records.<br>• There was no evidence to indicate that all standard operating procedures were reviewed at a minimum of every two years.<br>• An audit was not conducted every two years to verify that all activities comply with the *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* and SOPs. |
| S.55-63 - Records | Records were not always complete or accurate. For example:<br>a. On a form for surgery of deceased donors, the following was not completed on the form:<br>i. The Rh factor;<br>ii. A result for the VDRL test; and<br>iii. The rationale for exceptional distribution.<br>b. The abdominal flush solution was not indicated.<br>c. The blood group was indicated as "pos".<br>d. The full start date of the withdrawal from life support was not indicated.<br>e. On the SOP revision log, the date recorded for training of one of the SOP was prior to the revision date of the SOP. |
| S.64-69 - Personnel, Facilities, Equipment and Supplies | • A process for determining competency assessment had not been developed.<br>• There were a number of SOPs implemented where there were no records of training available. |
| Section 18 Donor Suitability Assessment | The date of completion of the donor medical and social history questionnaire was missing for donor XXXX, as required by section 12.3 of the CSA General Standard. |

# CHAPTER 3

# DRUG GOOD CLINICAL PRACTICES (GCP) INSPECTION PROGRAM

## BACKGROUND

In Canada, clinical trials of drugs are regulated by Health Canada under the authority of the *Food and Drugs Act* (Act) and Division 5 of Part C of the *Food and Drug Regulations: Drugs for Clinical Trials Involving Human Subjects* (Regulations), which includes the requirement for good clinical practices (GCP).

These Regulations provide the Minister with the authority to regulate the sale and importation of drugs used in clinical trials. Good clinical practices are further described in the *International Conference on Harmonization (ICH) Guidance, Topic E6 (ICH E6)*.

Every year, Health Canada inspects a sample of clinical trial sites in Canada to assess their compliance with these regulatory requirements, in accordance with the *Inspection Strategy for Clinical Trials* (POL-0030). The main objective of these inspections is the protection of the rights, safety, and well-being of the human subjects enrolled in clinical trials. Inspections are also conducted to verify the integrity of the data collected in clinical trials which may subsequently be submitted for evaluation at the next step in the drug's development, and eventually for marketing approval.

The Inspectorate is responsible for the selection of clinical trial sites for inspection in collaboration with the Therapeutic Products Directorate (TPD) and the Biologics and Genetic Therapies Directorate (BGTD). Selection of sites for inspection is based on risk and applies to all on-going or closed clinical trials in Canada.

## WHAT'S NEW?

In response to the audit on the *Regulation of Pharmaceuticals* conducted by the Office of the Auditor General in 2011, the GCP Inspection Program has revised its existing internal procedure for conducting clinical trial inspections.

While the methodology of the way inspections are conducted remains the same, specific timelines were established for key steps in the inspection process. These included deadlines for communication of inspection results, such as notifying regulated parties of non-compliant ratings, and the review of proposed corrective measures in response to inspection exit notices. The revised procedure was completed in June 2012 and was implemented in March 2013.

# INSPECTION RESULTS AND STATISTICS

## STATISTICS ON CLINICAL TRIAL SITE INSPECTIONS

Studies involving biological, pharmaceutical, and narcotic/controlled drug investigational products were inspected during the period covered in this report.

During the period covered in this report, qualified investigators (QIs) and sponsors at fifty (50) clinical trial sites were inspected. All but two (2) of the clinical trial sites inspected this past year were issued overall "C" inspection ratings. It is important to note that a compliant rating does not mean that there are no observations or corrective actions required. In both cases where a "NC" rating was assigned, the Inspectorate took action, including requiring the inspected parties to immediately correct the deficiencies, and recommending to the Health Canada directorate which issued the authorization, TPD or BGTD, that the authorization to conduct the inspected study be suspended or cancelled.

## MOST COMMON OBSERVATIONS CITED

A total of 463 observations were noted during the inspection of fifty (50) clinical trial sites in the fiscal year 2012–2013. Of the 463 observations cited against Division 5 of Part C, the vast majority, 95%, of these were cited against the ten sections, as shown in Figure 3.1 below.

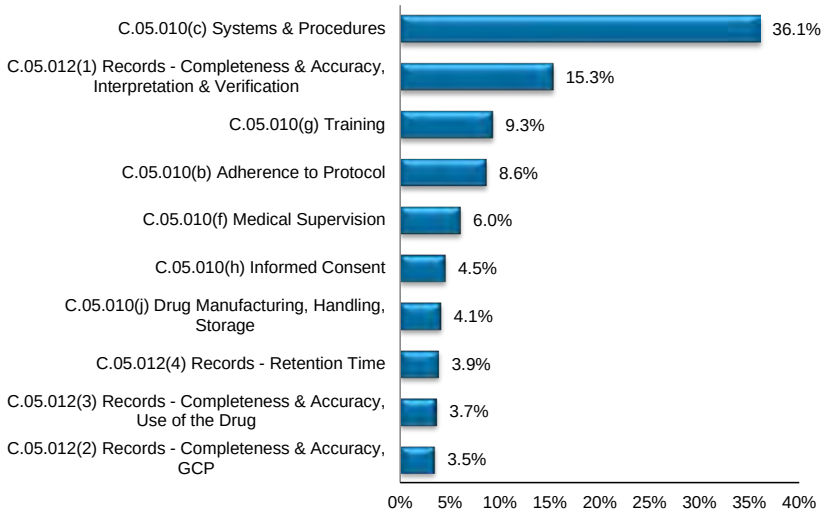


***Figure 3.1*** Sections of the Division 5 of Part C of the *Food and Drug Regulations* most commonly cited as a percentage of the total number of observations cited during inspections conducted nationally. (Fiscal Year: April 1, 2012 – March 31, 2013)

## RISK RATINGS OF OBSERVATIONS

Observations cited during inspections are classified as critical (Risk 1), major (Risk 2) and minor (Risk 3), based on the risk associated with the deviation from the Regulations, and in accordance with Health Canada's guidance document, *Classification of Observations Made in the Conduct of Inspections of Clinical Trials* (GUI-0043).

Of the 463 Risk observations issued, there were 223 Risk 3 (48%), 234 Risk 2 (51%), and six Risk 1 (1%) observations that were associated with Division 5 of Part C of the *Food and Drug Regulations*. During the period covered by this report, all of the Risk 1 observations cited were with respect to Section C.05.010(f), which requires that the sponsor must ensure, at each clinical trial site, that medical care and medical decisions, in respect of the clinical trial, are under the supervision of the qualified investigator.

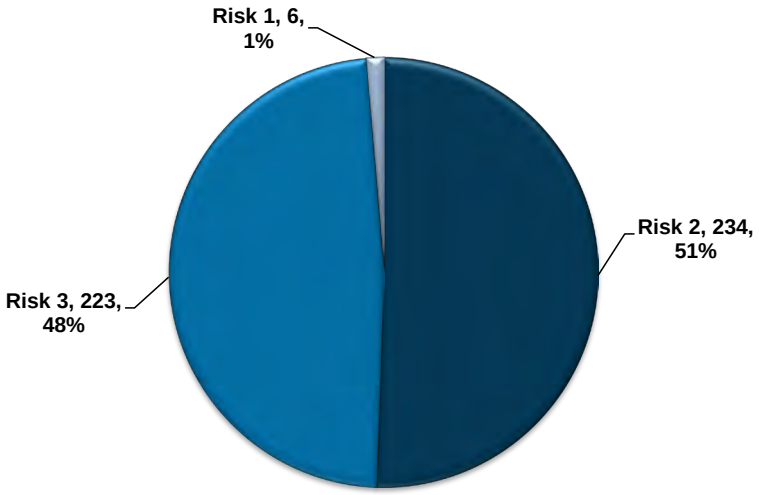


***Figure 3.2*** Distribution of risk ratings of observations during inspections conducted nationally. (Fiscal Year: April 1, 2012 – March 31, 2013)

## TABLE 3.1- EXAMPLES OF COMMON OBSERVATIONS CITED

| *Food and Drug Regulations* | Example of Observation |
|---|---|
| C.05.010(b)<br>Sponsor's Obligations<br>Adherence to Protocol | The clinical trial was not always conducted in accordance with the protocol. The following protocol deviations were noted: a) Visit (X) for Subject A was out of window; b) there were several cases where ECGs were performed after subject blood draws rather than before; c) Subject B did not have [specific blood analysis] performed because blood was not drawn at the applicable study visit; d) Visits Y and Z for subject C included a brief physical and neurological exam, however, as per protocol, these visits should have included complete physical and neurological exams. |
| C.05.010(c)<br>Sponsor's Obligations<br>Systems and Procedures | Systems and procedures that assure the quality of every aspect of the trial were not always implemented. For example, documentation was lacking to demonstrate the calibration and maintenance of equipment used in the study at the site.<br><br>Documentation is lacking to demonstrate that monitoring of the clinical trial site by the sponsor has been conducted. According to the monitoring SOP, monitoring, assignment of a monitor by the QI, and the first monitoring visit are to occur after enrolment of one or two subjects. There is no documentation that a monitor was assigned, and no monitoring visits have occurred for the trial to date, although several subjects had been enrolled at the time of the inspection. |
| C.05.010(f)<br>Sponsor's Obligations<br>Medical Supervision | Documentation was lacking to support that the qualified investigator's roles and responsibilities were met with respect to medical care and medical decisions for the study. For example, the subjects' medical histories were not taken and assessed by the qualified investigator as part of the required eligibility assessment; there was no documentation to support that the concomitant medication logs recorded by the study coordinator were ever reviewed by the qualified investigator as part of the eligibility assessment at randomization, and throughout the study; there was no documentation that eligibility assessments were reviewed by the physicians for all of the subjects randomized in the study, and there were also examples where the QI's sign-off did not happen, the sign-off was not dated, the sign-off happened before the subject's screening visit, or the sign-off was after subject's randomization in the study; there was no documentation to support that the physicians (QI or delegated physician sub-investigators) reviewed and assessed the information for visit 1, recorded by the study coordinators in the subjects' source documents, for determination of the subjects' eligibility; there was no documentation to support that the QI approved the dispensing of the study drug to the subjects at all visits after randomization. |
| C.05.010(g)<br>Sponsor's Obligations<br>Training | Documentation was lacking to demonstrate that all staff involved in the trial have been fully trained on the protocol and relevant procedures before the start of the trial. For example, no documentation was on file to show: that staff have been trained on the pharmacy Standard Operating Procedure (SOP) pertaining to the handling of the trial drug; that the study nurses attended the site initiation visit; that the QI was trained by the sponsor on how to assess Adverse Events (AEs) in accordance with the protocol (noting that the QI role in assessing AEs was stated in the Standard Operational Manual provided by the sponsor); and that the second pharmacist at the pharmacy (who was involved in maintaining the drug accountability log) was trained on relevant sections of the protocol.<br>It could not be verified that all individuals involved in the conduct of the clinical trial were qualified by training. For example: a) out of four study team members who were conducting subject telephone contacts, only one received training on this task, which was also delegated prior to receipt of training; b) an unblinded study coordinator was assigned protocol-related tasks as of [date], but did not receive training until two weeks later; c) most Standard Operating Procedures (SOPs) were implemented prior to staff training/review; d) there is one study team member who has never reviewed the applicable SOPs. |

## TABLE 3.1 - CONTINUED

| *Food and Drug Regulations* | Example of Observation |
|---|---|
| C.05.010(h)<br>Sponsor's Obligations<br>Informed Consent | Not all subjects were re-consented on updated versions of the informed consent form (ICF) in a timely manner. Specifically, subjects A and B were not re-consented on the consent form version [date], until six and three months later, respectively, although visits for each subject had occurred during this period. |
| C.05.010(j)<br>Sponsor's Obligations<br>Drug manufacturing, handling, storage | It could not be verified that study drug was maintained at its required storage temperature while in transit. Per manufacturer's specifications, the study drug is to be stored between 15-30°C. Stability data provided does not support shipment of the drug without a validated shipper or temperature monitoring device. The drug can be in transit for up to 5 days en route to the site. |
| C.05.012(1)<br>Sponsor's Obligations<br>Records – Completeness and accuracy, interpretation and verification | It could not be demonstrated that the sponsor has recorded all information with respect to the clinical trial in a way that allows its complete and accurate reporting as well as its verification. Specifically: a) The eligibility (inclusion/exclusion) criteria page was not signed and dated for any subject to indicate who performed the assessment; b) Vital Signs and Physical Examination sheets were not signed and dated for any subject to indicate who performed these assessments. |
| C.05.012(2)<br>Sponsor's Obligations<br>Records – Completeness and accuracy, GCP | The Sponsor did not maintain complete and accurate records to establish that the clinical trial was conducted in accordance with good clinical practices. For example: a) it could not be confirmed whether several subjects had the injection of study drug performed by the QI or a delegated surgeon, as such information was not documented in the surgical notes; b) it was not always documented who performed and recorded subject's clinical information on the study forms, when these were recorded, and if such information was reviewed at the study assessment time points, as no name, initials or signature were found on such source documents; c) Subject A did not receive study drug as no [study procedure] was performed during surgery; however, documentation was lacking to identify the status of this subject (e.g. screen fail, withdrawal from the study, etc.). |
| C.05.012(3)<br>Sponsor's Obligations<br>Records – Completeness and accuracy, use of the drug | Complete and accurate records in respect of the use of the drug were not maintained. For example: a) there was no record to document the temperature monitoring during the transportation of the study between the Hospital A pharmacy and the Hospital B pharmacy; b) the dispensing of Study drugs X and Y was noted on the chemotherapy chart of each subject, however, there were no accountability logs for either study drug, nor a destruction log for Study drug Y; c) documentation from the Hospital A pharmacy to confirm receipt of Study drug Z was incomplete and the following other documents were missing: TempTale tracing, packing slip, stability data, and a copy of the drug re-supply request. |
| C.05.012(4)<br>Sponsor's Obligations<br>Records – Retention time | The procedure for 25 year archiving of study records was missing the following elements: a) who has overall responsibility for the records and who would be responsible should the qualified investigator retire or move their practice; b) how record security is maintained, especially when files are in transit from the first to the second storage location; c) the length of time the records will be stored at each storage location; d) whether the sponsor is notified when there is a change in the archiving procedure (e.g. who is responsible, where files are stored). |

# CHAPTER 4

# DRUG GOOD MANUFACTURING PRACTICES (GMP) INSPECTION PROGRAM

## BACKGROUND

As part of the Inspectorate's role of delivering a national compliance and enforcement program, drug establishment inspections against the 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 in Canada.

To ensure a uniform application of these requirements and to help industry comply, the Inspectorate has developed a series of guides and other related documents, references to which can be found at the end of this report.

The Inspectorate is responsible for conducting inspections of establishments that are involved in 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*. These inspections are conducted to verify the compliance with GMPs (Part C, Division 2 of the *Food and Drug Regulations*) which is a requirement for the issuance of an Establishment Licence (Part C, Division 1A of the *Food and Drugs Regulations*).

Given the global nature of the drug manufacturing business, not all drug products available in Canada are manufactured in Canada. In fact, 80% of the drug products available on the Canadian market are imported into Canada. To ensure the safety of these drugs, Health Canada leverages inspections by trusted regulatory partners of facilities abroad, by conducting a review of their inspection reports in order to assess the GMP compliance of foreign sites that fabricate, package/label or test drugs that are to be imported into Canada. In cases where such inspections are not available for a given foreign site, an importer may request Health Canada to conduct an inspection. The decision to inspect a foreign site is based on several risk criteria such as the compliance history of the site, the nature of the drug products manufactured, the sterility status, the location, the date of the last inspection, the overall risk assigned to the site, etc. In 2012–2013, the Inspectorate conducted 800 drug foreign site paper reviews and Health Canada conducts on average 10-15 foreign site inspections per year.

## WHAT'S NEW?

On September 29, 2012, Health Canada proposed regulatory requirements amending the *Food and Drug Regulations* to extend Good Manufacturing Practices (GMP) requirements to active pharmaceutical ingredients (APIs). The proposed amendments were published in Part II of the *Canada Gazette* on May 08, 2013, and came into force on November 8, 2013. A new licensing framework and inspection program for APIs was introduced in the fall of 2013.

Health Canada has developed a guidance document entitled *Good Manufacturing Practices (GMP) for Active Pharmaceutical Ingredients (APIs)* (GUI-0104) designed to facilitate compliance by the regulated industry and to enhance consistency in the application of the new regulatory requirements for APIs.

## INSPECTION RESULTS AND STATISTICS

The initial inspection of an establishment conducting licensable activities is triggered by the receipt of a Drug Establishment Licence Application. 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.

A regular inspection is generally conducted within 12 months of the initial inspection. The date of any subsequent inspection depends on the activities being conducted by the establishment.

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. Between April 2012 and March 2013, the Inspectorate conducted 416 Drug GMP inspections.

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 from 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 an overall compliant "C" rating. Non-compliant "NC" ratings are issued to establishments that are deemed to be non-compliant with the GMP regulations. A "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.

Within the period covered in this report, a total of 416 inspections were conducted and 95% were found to be in compliance with the *Food and Drug Regulations*.

## STATISTICS ON LICENSED ESTABLISHMENTS

One establishment may be licensed for multiple activities, thus 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 Figure 4.1.

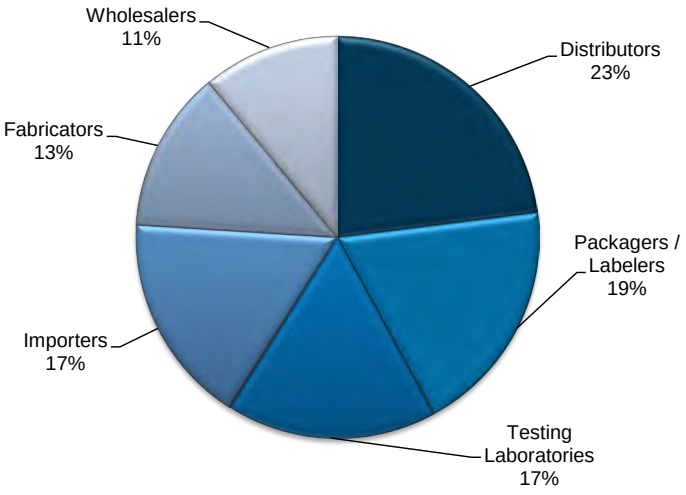


***Figure 4.1*** Proportion of Drug Establishment Licence (DEL) holders by activity. (Fiscal Year: April 1, 2012 – March 31, 2013)

## MOST COMMON OBSERVATIONS CITED

The highest number of Risk 1 observations were recorded under C.02.029 - Sterile Products, given the high risk associated with potential contamination of sterile products. This is consistently the regulation most cited for Risk 1 observations. (See *2006-2011 Drug GMP Inspection Summary Report*). The health risk of using a sterile injectable product of compromised quality is much greater than that of a non-sterile topical product. Although it is not always possible to show a direct link between noncompliance and product quality, departures from GMPs increase the likelihood of poor quality products being released for use by consumers.

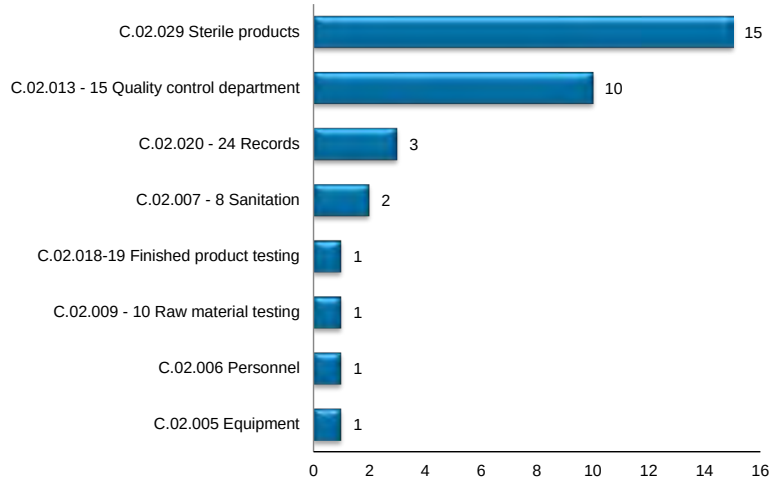


***Figure 4.2*** Sections of the *Food and Drug Regulations* cited as Risk 1 observations during inspections conducted nationally. (Fiscal Year: April 1, 2012 – March 31, 2013)

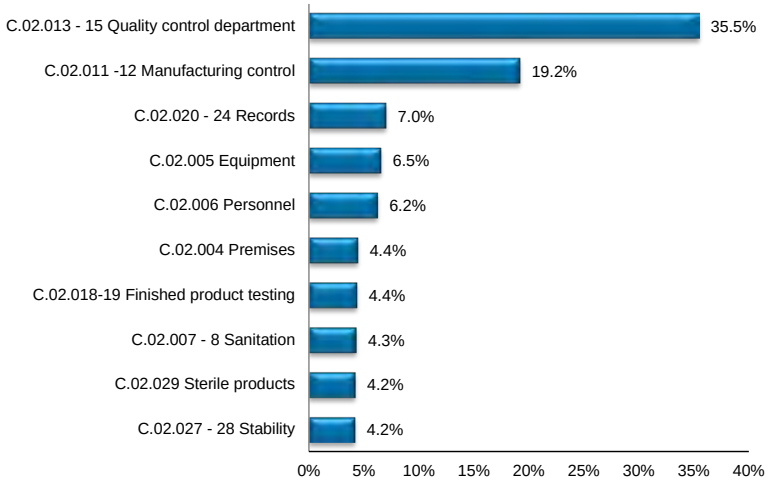


***Figure 4.3*** The top ten sections of the *Food and Drug Regulations* (FDR) most commonly cited as a percentage of the total number of observations cited during inspections conducted nationally. (Fiscal Year: April 1, 2012 – March 31, 2013)

## RISK RATINGS OF OBSERVATIONS

There is a relative stability in total number of observations per year and the percentage of Risk 2 ratings is consistently the highest of the three risk levels (See *2006-2011 Drug GMP Inspection Summary Report*).

During the 416 inspections a total of 3466 observations were noted. The majority of these observations were of Risk 3 and 2 (48% and 51% respectively) and the remaining observations were of Risk 1 (1%).

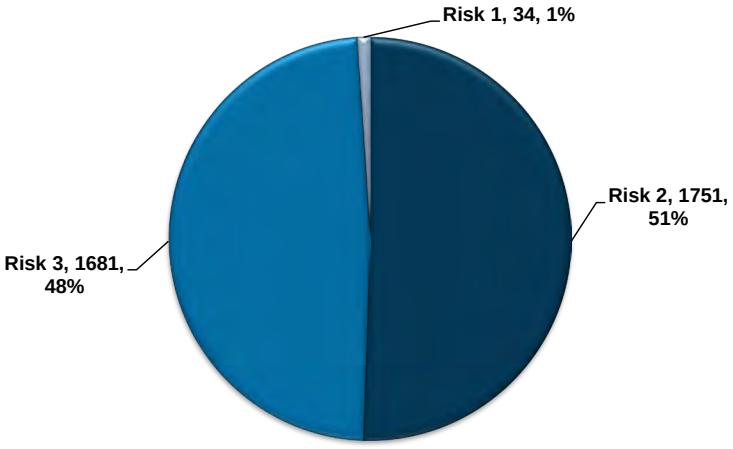


***Figure 4.4*** Distribution of risk ratings of observations during inspections conducted nationally. (Fiscal Year: April 1, 2012 – March 31, 2013)

## TABLE 4.1 - EXAMPLES OF COMMON OBSERVATIONS CITED

The regulations against which the majority of observations are cited are C.02.013-15 (Quality Control Department), and C.02.011-12 (Manufacturing Control).

Examples of common observations cited, attributed to individual sections of *Food and Drug Regulations*, are as follows:

| *Food and Drug Regulations* | Example of Observation |
|---|---|
| C.02.011<br>Manufacturing Control | • Process Validation for critical production processes not conducted or incomplete<br>• Incomplete manufacturing procedures / batch documents; failure to follow manufacturing procedures<br>• Incomplete Packaging Documents or Procedures |
| C.02.012<br>Manufacturing Control | • Inadequate/Lack of Quality Agreements<br>• Inadequate/Lack of Recall system/procedure<br>• Absence of/ inadequate Self Inspection Program |
| C.02.015<br>Quality Control Department | • Inappropriate procedures for handling storage and shipment of drug products with respect to temperature requirements<br>• Laboratory Operations issues |

# CHAPTER 5

# DRUG GOOD PHARMACOVIGILANCE PRACTICES (GVP) INSPECTION PROGRAM

## BACKGROUND

**As part of Health Canada's mandate to maximize the safety, quality and efficacy of health products, on August 1, 2004, Health Canada implemented an inspection program for Good Pharmacovigilance Practices (GVP), previously known as Post-Market Reporting Compliance (PMRC).**

The GVP inspection program is intended to verify that manufacturers meet 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*, including but not limited to the reporting of adverse drug reactions (ADR) and unusual failure in efficacy of new drugs, as well as the preparation of annual summary reports to analyze whether there has been a significant change in what is known about the risks and benefits of the drug. These regulations are enforced to verify that manufacturers enact and maintain a rigorous ADR management program. ADR recording, analysis, and reporting are an integral part of the ongoing drug safety surveillance paradigm known as "pharmacovigilance". The continuous application of Good Pharmacovigilance Practices serves to ensure that marketed drugs remain safe and effective well after their market authorization.

Within the context of the GVP inspection program, Market Authorization Holders (MAH) and importers of drug products are both subject to inspections. MAH and importers' names appear on product labels, and as such, they may receive Adverse Drug Reactions (ADRs) from other companies or consumers. The following drugs marketed in Canada for human use are subject to GVP inspections: pharmaceuticals; biologics, including biotechnology products, vaccines and fractionated blood products; medical gases; and radiopharmaceuticals.

To promote a uniform application of the requirements, and to help the industry to comply with them, the Inspectorate has developed guidance documents which have been listed at the end of this report.

## WHAT'S NEW?

On February 11, 2013, one new and two revised guidance documents relating to the GVP inspection program were posted on Health Canada's website.

The new guidance document, entitled *Good Pharmacovigilance Practices (GVP) Guidelines* (GUI-0102), provides interpretive guidance to industry on the expectations of inspectors with respect to the adverse drug reaction and post-approval reporting requirements when conducting GVP inspections. These guidelines are designed to facilitate compliance by the regulated industry and to enhance consistency in the application of the regulatory requirements regarding good pharmacovigilance practices.

## INSPECTION RESULTS AND STATISTICS

The Inspectorate program is responsible for the selection of sites for inspection. The guiding principle in the selection process is the safety and efficacy of drugs marketed in Canada. Various criteria may be considered, but, ultimately, Health Canada must mitigate the greater risk to health. The selection of establishments subject to GVP inspection is based on

a variety of criteria including, but not limited to the following: compliance history of the establishment, information on the relevant drug products, and reported adverse drug reactions.

The duration of these inspections varies depending on the type of activities, the number of drug products, and the volume of adverse drug reactions.

During an inspection, the inspector will record all deviations from the requirements outlined in sections C.01.016 to C.01.020, C.08.007(h) and C.08.008(c) of Part C of the *Food and Drug Regulations* as observations in the Inspection Exit Notice. Each observation is assigned a risk rating of critical (Risk 1), major (Risk 2), or minor (Risk 3) as per the principles and guidelines set forth in the *Risk Classification of Good Pharmacovigilance Practices (GVP) Observations* (GUI-0063). Depending on the severity of the observations, i.e. the nature and extent of the deviation, an overall rating of Compliant ("C") or Non-Compliant ("NC") is issued to the establishment. It is important to note that a compliant rating does not mean that there are no observations or corrective actions required.

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). During the course of an inspection, an inspector may face situations of non-compliance. These situations are assessed according to Health Canada's risk determination principles and appropriate compliance and enforcement actions may be taken.

Within the period covered in this report, a total of 82 inspections were conducted and all were found to be in compliance with the *Food and Drug Regulations*; however, concerns were raised during several inspections and re-assessments will be conducted in 2013–2014. Re-assessments are follow-up inspections 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.

## MOST COMMON OBSERVATIONS CITED

As per Figure 5.1, the top three observations noted were: Serious Adverse Drug Reaction Reporting - C.01.017, (reporting by the manufacturer of serious ADR that has occurred in Canada and serious unexpected ADR that has occurred outside Canada within 15 days after receiving or becoming aware of the information), Annual Summary Report and Case Reports - C.01.018 (preparation of annual summary report by the manufacturer to analyze whether there has been a significant change in what is known about the risks and benefits of the drug) and Prohibition - C.01.016 (prohibition to sell a drug unless the manufacturer complies with the requirements regarding ADR reporting and the preparation of annual summary report).

Of note, a small number were cited under C.08.008(c) Efficacy, which is to be expected, given the fact that not all establishments inspected were involved with new drugs. Section C.08.008(c) of the *Food and Drug Regulations* sets out requirements to report unusual failure in efficacy for new drugs.

An unusual failure in efficacy is when 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.

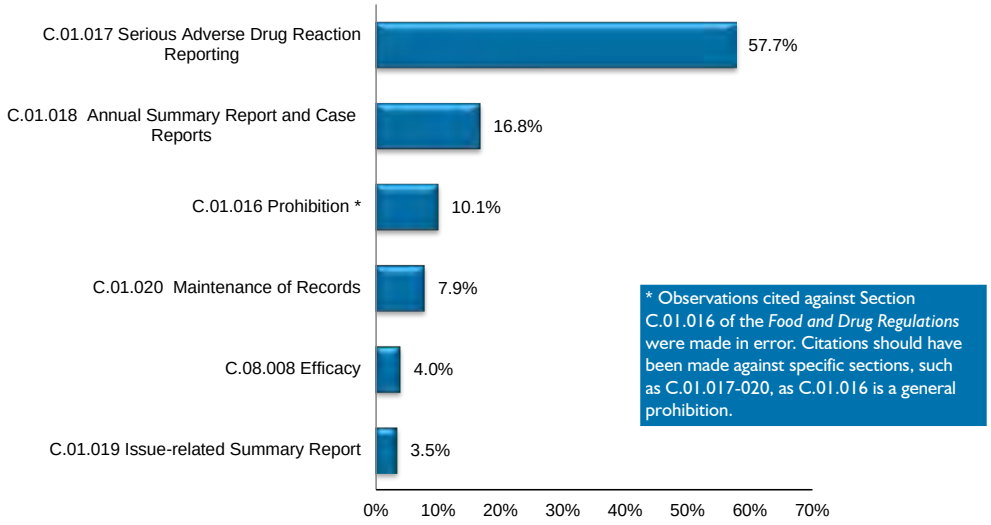


***Figure 5.1*** Sections of the *Food and Drug Regulations* most commonly cited as a percentage of the total number of observations cited during inspections conducted nationally. (Fiscal Year: April 1, 2012 – March *31, 2013)*

## RISK RATINGS OF OBSERVATIONS

A total of 227 observations were noted during the inspection of 82 establishments in the fiscal year 2012–2013. Please note that deviations of the same nature may be contained in one observation. Observations were mostly assigned Risk 2 (54%) and Risk 3 (46%) ratings. No Risk 1 observations were noted in this fiscal year. Corrective actions proposed in response to the observations were found to be acceptable in all cases, and a "C" rating was assigned to every establishment inspected.

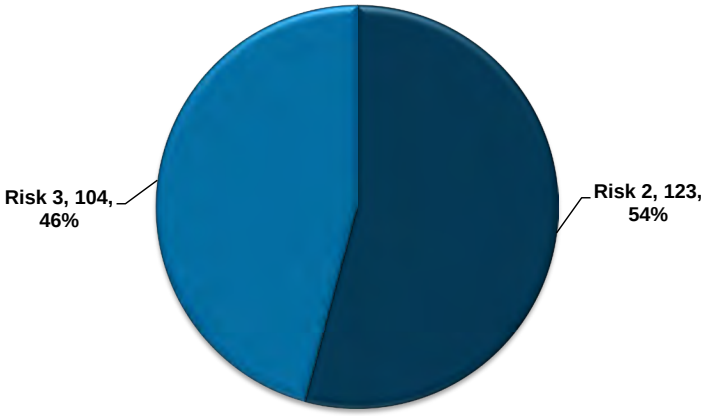


***Figure 5.2*** Distribution of risk ratings of observations during inspections conducted nationally. (Fiscal Year: April 1, 2012 – March 31, 2013)

## TABLE 5.1 - EXAMPLES OF COMMON OBSERVATIONS CITED

| *Food and Drug Regulations* | Example of observation |
|---|---|
| Efficacy - C.08.008 | • Not all domestic cases of unusual failure in efficacy for new drugs had been reported to Health Canada within 15 calendar days of initial receipt of the information by the MAH.<br>• The company did not perform any assessment of lack of efficacy cases and did not provide any justification on why those lack of efficacy cases were not reported to Health Canada. |
| Serious Adverse Drug Reaction Reporting - C.01.017 | • There were no systems or written procedures which would demonstrate that the firm could effectively receive, evaluate and report adverse drug reactions to Health Canada.<br>• Several foreign reports of serious unexpected ADRs were not submitted within 15 days of awareness by the firm.<br>• Not all domestic serious adverse drug reactions were reported to Health Canada within 15 calendar days after receiving or becoming aware of the information. |
| Annual Summary Report and Case Reports - C.01.018 | • Annual Summary Reports were not prepared for all of the firm's DIN products.<br>• There is no written procedure in place describing the process for preparing annual summary reports. |
| Issue-related Summary Report - C.01.019 | • There is no written procedure in place describing the process for preparing issue-related summary reports. |
| Maintenance of Records - C.01.020 | • There was no evidence that pharmacovigilance records were retained for 25 years after the day on which they were created, as required by the Regulations.<br>• There is no written procedure in place describing the process for maintenance of ADR records. |

# CHAPTER 6

# MEDICAL DEVICES INSPECTION PROGRAM

## BACKGROUND

Health Canada's Inspectorate Program has the role of delivering a national compliance and enforcement program for medical devices. The authority to deliver this program is derived from the *Food and Drugs Act* (Act) and the *Medical Devices Regulations* (Regulations).

It is within this context that licensed manufacturers, importers, and distributors of medical devices are inspected. The medical device inspection program was initiated in March 2004, and the selection of companies for inspection is based on risk. Both the medical devices being sold and the activities conducted by the establishment (i.e. manufacturing, importing and/or distributing) are considered. With respect to activities conducted by an establishment, distributing and importing are considered to be associated with a lower risk than manufacturing. Companies conducting multiple activities are categorized by their highest risk activity. For example, a company that manufactures and imports medical devices is categorized as a manufacturer.

Medical device inspections consist of a pre-inspection review of relevant company information, the actual inspection of the company, and a post-inspection follow-up where a report listing the observed non-compliances is presented to company representatives and corrective actions are discussed. The inspections assess an establishment's conformity with the relevant sections of the Act and Regulations. The document, *Guidance on the Medical Devices Inspection Program* (GUI-0064) provides guidance on the interpretation of the Regulations.

In 2010, a risk rating scheme was implemented in the inspection program, whereby observations are assigned a ranking of Risk I (highest), Risk 2 or Risk 3. Based on the combination of the number and types of observations noted, a company is given an overall rating of compliant ("C") or non-compliant ("NC").

## WHAT'S NEW?

For the 2012–2013 fiscal year, the Medical Devices Inspection Program introduced an inspection cycle for domestic Medical Device Establishment Licence (MDEL) holders. This stipulates that Canadian manufacturers, importers and distributors of medical devices will be inspected every three, four and five years, respectively. In addition, resources will be dedicated to the inspection of new establishments and the re-inspection of establishments that have received a non-compliant rating.

Prior to the introduction of an inspection cycle, Health Canada inspectors were focused on visiting medical device establishments for the first time. The inspections were prioritized based on several risk factors including the activities being conducted, the devices being sold and the size of the company.

Also in the 2012–2013 fiscal year, Health Canada initiated a pilot project to evaluate expanding the scope of the medical device inspection program to encompass foreign establishments, which had previously not been included in the program. This pilot project was conducted to gain insight into the level of compliance of foreign establishments and their understanding of the Regulations and the Act, and to explore options for conducting foreign inspections.

# INSPECTION RESULTS AND STATISTICS

## STATISTICS ON LICENSED ESTABLISHMENTS

The number of MDEL holders constantly fluctuates due to licence withdrawal/cancellation, as well as new licence applicants.

As of the start of the 2012–2013 fiscal year, there were 2057 domestic and foreign MDEL holders, which are classified by their highest-risk activity.

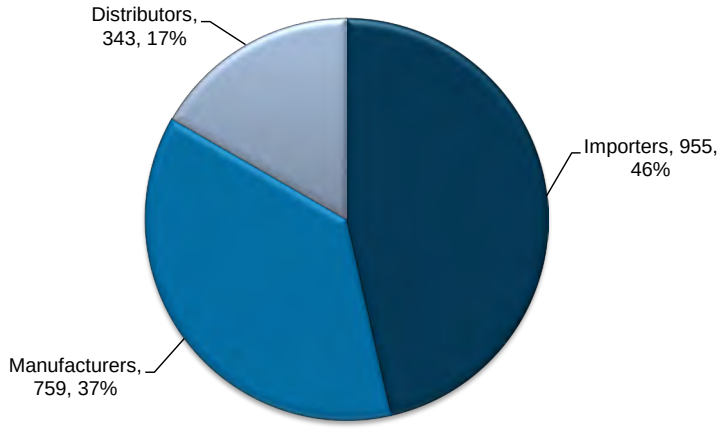


***Figure 6.1*** Proportion of Medical Device Establishment Licence (MDEL) holders who are identified as manufacturers, importers, and distributors (Fiscal Year: April 1, 2012 – March 31, 2013)

Importers make up the largest number of the MDEL holders (46%), followed by manufacturers (37%), and distributors (17%). About half of the manufacturers and distributors are located outside of Canada.

All of the licensed establishments located both in Canada and abroad are assigned to one of the Inspectorate Program's six regional offices based on geographical location (Atlantic, Quebec, Ontario, Prairie [Manitoba/Saskatchewan and Alberta] and BC). Of these regions, Ontario is responsible for the greatest number of companies.

## INSPECTION STATISTICS

For fiscal year 2012–2013, 596 inspections were conducted. Most of the inspections were of medical device importers (336), followed by manufacturers (199) and distributors (61).

The overall compliance rate was high at 98%, with 12 establishments receiving a non-compliant rating.

A total of 3251 observations were included in the inspection reports, resulting in an average of 5.5 observations per inspection. This is consistent with what was found during the analysis of the Inspection Program for the years from 2004 to 2009, which covered over 700 inspections (see *Summary of the Results of the Medical Devices Inspections Program from 2004–2009*).

## MOST COMMON OBSERVATIONS CITED

Of the 3251 observations cited against the Act and Regulations, over half were cited against four sections of the Regulations, as shown in Figure 6.2 below.

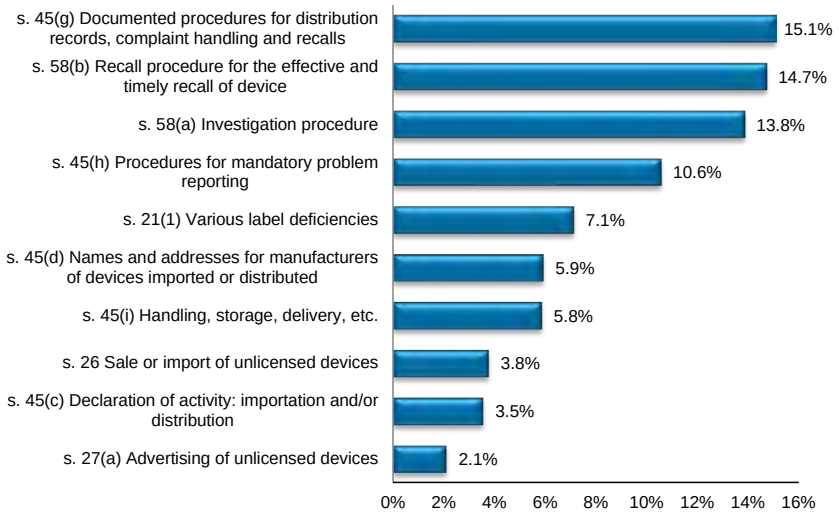


***Figure 6.2*** Sections of the *Medical Devices Regulations* most commonly cited as a percentage of the total number of observations cited during inspections conducted nationally. (Fiscal Year: April 1, 2012 – March 31, 2013)

The nature of the observations was similar to what was previously seen from 2004 to 2009. Most of the observations were related to deficiencies in written procedures pertaining to distribution records, complaint handling and recalls (s.45(g)), recall procedure (s. 58(b)), investigation of complaints (s.58(a)), and mandatory problem reporting (s. 45(h)). Collectively, these four sections of the Regulations account for over half of the total observations.

Other sections of the Regulations that were commonly observed to be in non-compliance, albeit to a lesser degree, typically involved those pertaining to labeling and establishment licensing. The frequency of observations related to the sale or import of unlicensed devices (s.26) is about half that of what it was during the period from 2004 to 2009 (3.8% vs. 6.9% of total observations or ~20% vs. ~40% of inspected MDEL holders – see *Summary of the Results of the Medical Devices Inspections Program From 2004–2009*).

This is significant as this section of the Regulations accounts for the greatest number of Risk 1 observations (see Figure 6.4 on following page).

Other sections of the Regulations associated with Risk 1 observations were those related to the adequacy of the distribution records as it relates to the ability to conduct an efficient product withdrawal from the market (s.53), the maintenance of distribution records (s.52(1)), the reporting of recalls to the Minister (s.64), and complaint investigation procedures (s.58(a)).

## RISK RATINGS OF OBSERVATIONS

Observations cited during inspections are classified as critical (Risk 1), major (Risk 2) and minor (Risk 3), based on the risk associated with the deviation from the Regulations, and in accordance with Health Canada's *Guidance on the Medical Devices Inspection Program* (GUI-0064). During the 596 inspections, a total of 3251 observations were noted. The majority of these observations were of Risk 3 and 2 (31% and 69% respectively) and the remaining observations were of Risk 1 (~1%).

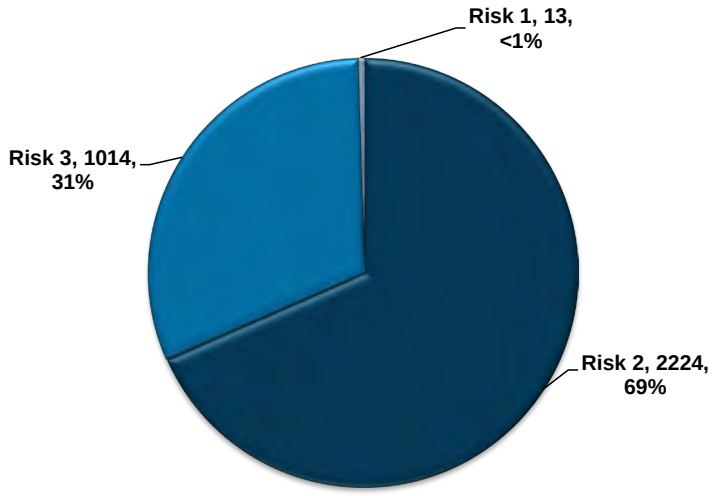


***Figure 6.3*** Distribution of risk ratings of observations during inspections conducted nationally. (Fiscal Year: April 1, 2012 – March 31, 2013)

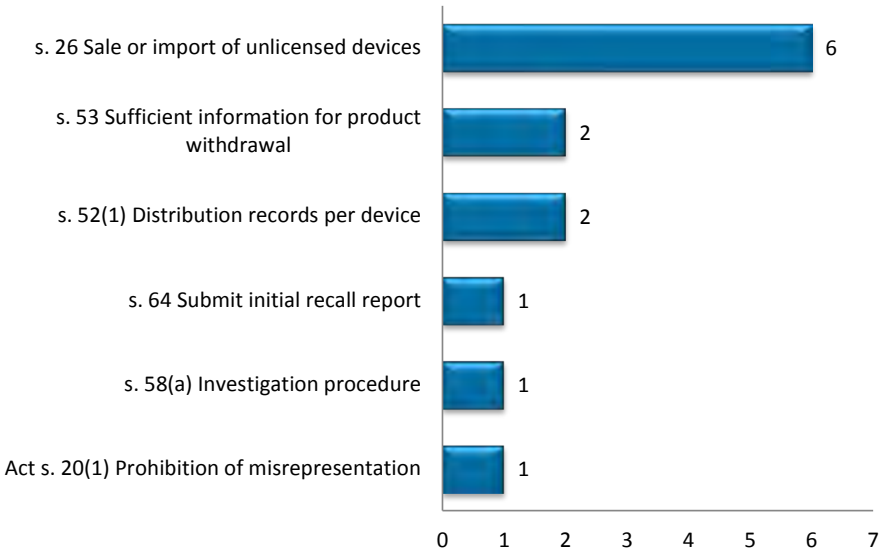


***Figure 6.4*** Sections of the *Medical Devices Regulations* or *Food and Drugs Act* (Act where indicated) cited as Risk 1 observations during inspections conducted nationally. (Fiscal Year: April 1, 2012 – March 31, 2013)

## TABLE 6.1 - EXAMPLES OF COMMON OBSERVATIONS CITED

| *Medical Devices Regulations* | Example of observation |
|---|---|
| s.45(g)<br>Distribution Records, Complaint Handling, and Recalls | The retention period for distribution records of electronic and hard copies (sales order) was not clearly described in the written procedure. |
| s.45(h)<br>Mandatory Problem Reporting | The company's procedure does not address the requirements of the following sections of the *Medical Devices Regulations*: s.60(1): Preliminary Reporting Timeframe, s.60(2): Contents of Preliminary Report, s.61: Contents of Final Report. |
| s.58(a)<br>Investigation Procedure | The company's procedure for complaint handling does not address the requirements of the following Regulations: s.58(a): Timelines for Effective and Timely investigation, s.57(1)(a): Maintain Records of Reported Problems, s.57(1)(b): Maintain Records of Actions Taken by the Manufacturer, Importer, or Distributor. |
| s.58(b)<br>Recall Procedure | The current procedure does not address the requirements of the following section of the *Medical Devices Regulations*: s.58(b): Effective and Timely Recall. |

# CHAPTER 7

# SEMEN INSPECTION PROGRAM

## BACKGROUND

In Canada, donor semen for assisted conception is regulated by Health Canada as a drug under the authority of the *Food and Drugs Act* (Act) and the *Processing and Distribution of Semen for Assisted Conception Regulations* (Semen Regulations). The purpose of the Semen Regulations is to reduce the potential risk of transmitting infectious agents through the use of donor semen in assisted conception.

Health Canada inspects all known processors, importers and/or distributors of donor semen intended for use in assisted conception in Canada to assess their compliance with the Semen Regulations. The frequency of donor semen inspections is outlined in the *Inspection Strategy for Semen Establishments* (POL-0023).

In accordance with POL-0023, regular inspections conducted by Health Canada are announced; however, unannounced inspections may be considered in situations where it is anticipated that this approach will provide a more accurate compliance assessment or when an immediate risk to health and safety has been identified.

During the period covered in this report, a total of 39 out of 113 active processors, distributors and importers of donor semen were inspected. All but one donor semen establishment were found to be overall compliant with the Semen Regulations. In the case of the non-compliant semen establishment, Health Canada took appropriate compliance and enforcement measures to prevent the distribution of non-compliant donor semen.

## INSPECTION RESULTS AND STATISTICS

### STATISTICS ON ACTIVE DONOR SEMEN ESTABLISHMENTS

In accordance with the Semen Regulations, processors and importers of donor semen must give a written notice to Health Canada at least 10 days before the date on which they begin processing or importing donor semen, and within 90 days of ceasing these activities. Distributors (including physicians) of donor semen are not required to provide Health Canada with notices of their intent to distribute or cease distribution of donor semen; however, they must ensure that all donor semen they intend to distribute has been processed in accordance with sections 9 to 11 of the Semen Regulations. Figure 7.1 illustrates the total number of donor semen establishments in Canada.

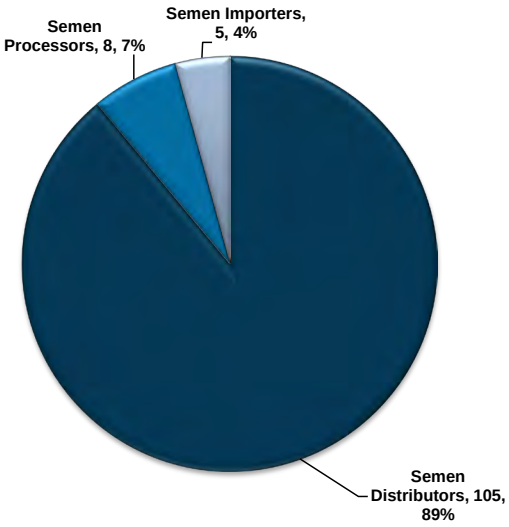


***Figure 7.1*** National distribution of the three types of (active) semen establishments. (Fiscal Year: April 1, 2012 – March 31, 2013)

It is important to note that some donor semen establishments conduct more than one activity. For the purpose of this report the number of establishments counted was based on the activities conducted. For example, an establishment that processes as well as imports donor semen is counted as both a processor and an importer. Furthermore, the number of donor semen distributors may fluctuate throughout the year as they are not required to notify Health Canada of their intent to start or stop distributing donor semen.

A total of 39 regular inspections of semen establishments were conducted during the period covered by this report. All active donor semen processors and importers were inspected. For example, of the eight known processors in Canada, it was determined that five had processed donor semen since the last Health Canada inspection and hence were inspected.

As described in POL-0023, final distributors (physicians) are inspected every five years and therefore not all active distributors were inspected during the period covered by this report.

An establishment that conducts more than one activity will be inspected depending on the status of those activities. For example, if an establishment imports and processes donor semen but has not imported any donor semen since the last inspection by Health Canada, the establishment will only be inspected for its processing activities.

## MOST COMMON OBSERVATIONS CITED

Figure 7.2 illustrates the prevalence of observations associated with the different sections of the Semen Regulations. The majority of observations were cited against Distributor Records S.13, followed by Processor Records S.12, and Screening S.9.

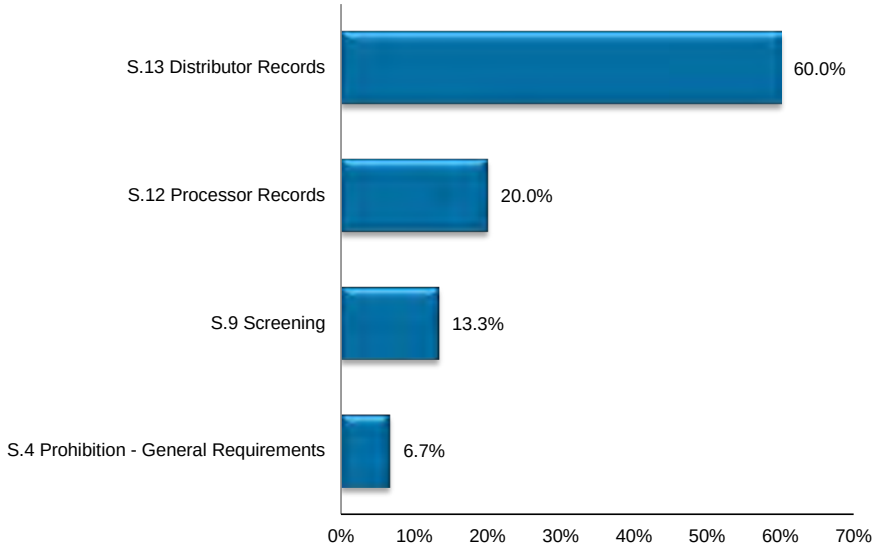


***Figure 7.2*** Sections of the *Processing and Distribution of Semen for Assisted Conception Regulations* (Semen Regulations) most commonly cited as a percentage of the total number of observations cited during inspections conducted nationally. (Fiscal Year: April 1, 2012 – March 31, 2013)

## RISK RATINGS OF OBSERVATIONS

Observations cited during inspections are classified as critical (Risk 1), major (Risk 2) or minor (Risk 3), based on the severity of the deviation from the Semen Regulations. The number and type of observations noted are taken into account when assigning the inspection an overall compliant ("C") or non-compliant ("NC") rating. It is important to note that an overall compliant rating does not mean that there were no observations or corrective actions required.

All importers and distributors of donor semen inspected during the period covered by this report were assigned an overall compliant rating. Four of the five donor semen processors inspected were assigned an overall compliant rating. In the case of the non-compliant rating, Health Canada took appropriate compliance and enforcement action, including measures to prevent the distribution of non-compliant donor semen.

During the 39 inspections, a total of 15 observations were noted. The majority of these observations were of Risk 3 and 2 (40% each) and the remaining observations were of Risk 1 (20%).

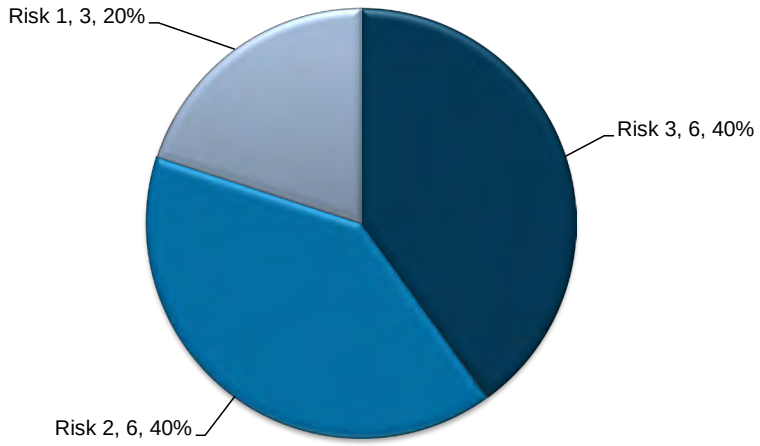


***Figure 7.3*** Distribution of risk ratings of observations during inspections conducted nationally. (Fiscal Year April 1, 2012 – March 31, 2013)

## TABLE 7.1 - EXAMPLES OF COMMON OBSERVATIONS CITED

| *Semen Regulations* | Example of observations |
|---|---|
| Section 4<br>Prohibition – General Requirements | After the semen was quarantined for a minimum of six months, the establishment did not determine that the donor was still not within a group set out under the heading "Exclusions" in clause 2 of the Directive. This is contrary to section 4.2.2(a) of Health Canada Directive: Technical Requirements for Therapeutic Donor Insemination. |
| Section 9<br>Screening | Although the donor answered yes to the question "During the past 12 months, have you had sex with someone whose sexual background you are unsure of? ", the donor was not excluded. However, none of the donated semen samples were inseminated. |
| Section 12<br>Processor Records | Although the SOP noted that all semen samples were to be destroyed when the semen culture was positive for any organisms not considered normal flora, it did not provide any instructions on how to determine whether or not an organism is considered normal flora. |
| Section 13<br>Distributor Records | The information, e.g., name and address of establishment, to whom 3 vials from donor XXX lot number XXX were sent, were incompletely documented.<br><br>The corrective action for one of the observation issued during the previous inspection, which required that the establishment obtain missing donor record, was incomplete in that the record of declaration of compliance by the processor was not available. |

# DEFINITIONS

**Compliant ("C"):** 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* and its associated Regulations. Inspections are routinely conducted on a predetermined cycle or as required to assess compliance.

**Non-compliant ("NC"):** 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 (Blood):** A deviation or deficiency to the *Food and Drugs Act* or Part C, Divisions 2 or 4 of the *Food and Drugs Regulations* noted during the inspection of a blood establishment and that is documented in the Exit Notice. The observations are classified as Risk 1, Risk 2 or Risk 3.

**Observation (GVP):** 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 Risk 1, Risk 2 or Risk 3.

**Observation (GMP):** 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 inspection Exit Notice. The observations are classified as Risk 1, Risk 2 or Risk 3.

**Observation (Medical Devices):** A state of deviation or deficiency with a specific requirement of the *Food and Drugs Act* or the *Medical Device Regulations* noted by an inspector during an inspection of a medical device establishment, that is confirmed in writing to the establishment in the Inspection Report. The observations are classified as Risk 1, Risk 2 or Risk 3.

**Observation (Semen):** A deviation or deficiency to the *Food and Drugs Act* or the Semen Regulations including the referenced sections of the Directive noted during the inspection of a processor, importer or distributor of donor semen for assisted conception and that is documented in the Exit Notice. The observations are classified as Risk 1, Risk 2 or Risk 3.

**Critical observation (Risk 1):** 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 drug safety information. Observations that involve fraud, misrepresentation or falsification under the *Food and Drugs Act* and Regulations of data are also considered critical.

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

**Minor observation (Risk 3):** An observation that is classified as not critical or major, but which indicates a deficiency and/or deviation from Division 5 of the *Food and Drug Regulations*.

# REFERENCES

## CHAPTER 1 - BLOOD INSPECTION PROGRAM


1. *Food and Drugs Act*
2. *Food and Drug Regulations*
3. *Inspection Strategy for Blood and Source Plasma Establishments* (POL-0039)
4. *Risk Classification of Observations made during Inspections of Blood Establishments* (GUI-0061)
5. *Compliance and Enforcement Policy* (POL-0001)


## CHAPTER 2 - CELLS, TISSUES AND ORGANS (CTO) INSPECTION PROGRAM


1. *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* (CTO Regulations)
2. *Guidance Document for Cells, Tissues and Organs Establishments - Safety of Human Cells, Tissues and Organs for Transplantation*
3. *Compliance and Enforcement Policy* (POL-0001)
4. *Guidance on Classification of Observations for Inspection of Cells, Tissues and Organs Establishments* (GUI-0101)
5. *Inspection Strategy for Cells, Tissues and Organs Establishments* (POL-0057)
6. *Food and Drugs Act*


## CHAPTER 3 - DRUG GOOD CLINICAL PRACTICES INSPECTION PROGRAM


1. *Inspection Strategy for Clinical Trials* (POL-0030)
2. *Guidance Document - Annex 13 to the Current Edition of the Good Manufacturing Practices - Guidelines Drugs Used in Clinical Trials* (GUI-0036)
3. *International Conference on Harmonization (ICH) Guidance, Topic E6* (ICH E6)
4. *Risk Classification of Observations in Clinical Trials* (GUI-0043)
5. *Guidance on the Retention of Records for Clinical Trials* (GUI-0068)


## CHAPTER 4 - DRUG GOOD MANUFACTURING PRACTICES INSPECTION PROGRAM


1. *Good Manufacturing Practices Guidelines* (GUI-0001)
2. *Risk Classification of GMP Observations* (GUI-0023)
3. *Good Manufacturing Practices (GMP) for Active Pharmaceutical Ingredients (APIs)* (GUI-0104)
4. *Compliance and Enforcement Policy* (POL-0001)
5. *GMP and Establishment License Enforcement Directive* (POL-0004)
6. *GMP Inspection Policy for Canadian Drug Establishments* (POL-0011)
7. Drug Establishment Good Manufacturing Practices - Pre-Application Package (Importers, Distributors and Wholesalers)

## CHAPTER 5 - DRUG GOOD PHARMACOVIGILANCE PRACTICES INSPECTION PROGRAM

1. *Guidance Document for Industry – Reporting Adverse Reactions to Marketed Health Products*
2. *ICH Harmonised Tripartite Guideline, Clinical Safety Data Management: Periodic Benefit-Risk Evaluation Report E2C(R2)* (2012)
3. *Inspection Strategy for Good Pharmacovigilance Practices* (GVP) for Drugs (POL-0041)
4. *Good Pharmacovigilance Practices (GVP) Guidelines* (GUI-0102)
5. *Risk Classification of GVP Observations* (GUI-0063)
6. *International Conference on Harmonisation, Post-Approval Safety Data Management: Definitions and Standards for Expedited Report (ICH E2D)* 2003

## CHAPTER 6 - MEDICAL DEVICES INSPECTION PROGRAM

1. *Food and Drugs Act*
2. *Medical Devices Regulations*
3. *Guidance on the Medical Devices Inspection Program* (GUI-0064)
4. *Summary of the Results of the Medical Devices Inspections Program from 2004–2009*

## CHAPTER 7 - SEMEN INSPECTION PROGRAM

1. *Guidance on the Processing and Distribution of Semen for Assisted Conception Regulations* (GUI-0041)
2. *Guidance on Donor Semen Special Access Programme: Donor Semen Eligible for Special Access*
3. *Inspection Strategy for Semen Establishments* (POL-0023)
4. *Risk Classification of Observations to Donor Semen Establishments* (GUI-0053)
5. *Processing and Distribution of Semen for Assisted Conception Regulations*


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