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INSPECTORATE PROGRAM

ANNUAL INSPECTION SUMMARY REPORT

2013 – 2014

Canada

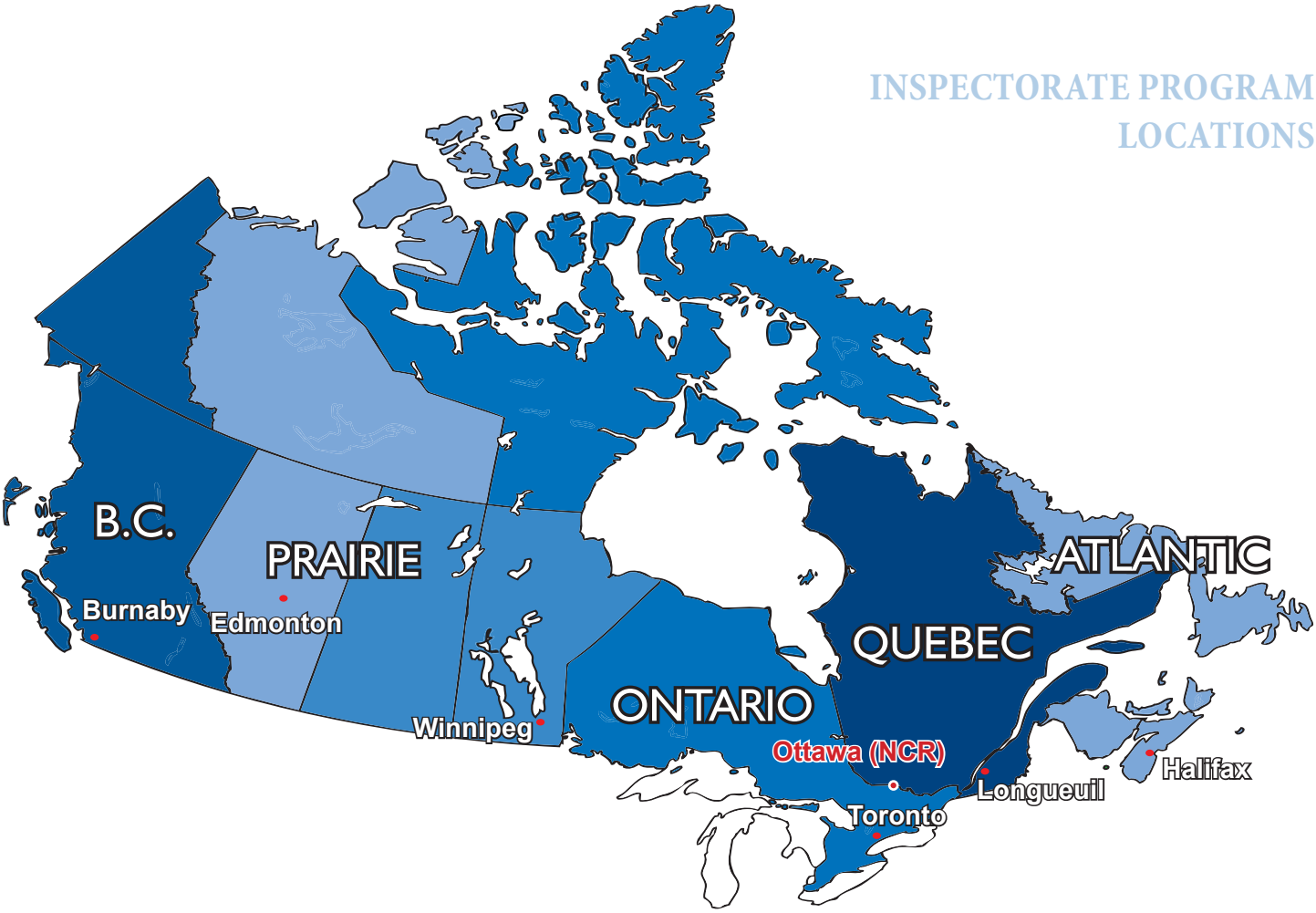
OUR VISION

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.

INSPECTORATE PROGRAM LOCATIONS



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 not intended to provide legal advice regarding the interpretation of the Act or Regulations. If a regulated party has questions about their legal obligations or responsibilities under the Act or Regulations, they should seek the advice of legal counsel.

MESSAGE FROM THE DIRECTORS GENERAL

We are pleased to present the Health Canada Inspectorate Program Annual Inspection Summary Report for 2013-2014. 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. The inspection activities outlined in this report support the Department's mandate to help the people of Canada maintain and improve their health by ensuring the safety and efficacy of health products available in Canada. This report also continues our commitment to transparency by making compliance information readily available to Canadians.

As evidenced in this report and the 2012-2013 Annual Inspection Summary Report, the health product industry in Canada has a high level of compliance with the *Food and Drugs Act* and its associated Regulations. In 2013-2014 the overall compliance rating of the Canadian health product industry was 98%. Similarly, in 2012-2013 the Canadian health product industry compliance rating was 97%, demonstrating a consistently high level of compliance in Canada.

This report outlines inspection activities conducted by the Inspectorate for the fiscal year (FY) 2013-2014. Inspection results are summarized by product line and inspection type, and are explained according to relevant regulatory requirements. In total, Health Canada conducted 1,238 on-site inspections in Canada, made thousands of observations requiring corrective actions, and issued 30 non-compliant (NC) ratings.

In each chapter you will find the key priorities for each inspection program for 2014-2015. These priorities support the Department's commitments and vision for the regulation of health products in Canada. The key priorities for all inspection programs are to: 1) enhance the risk-based approach to regulatory oversight by modernizing legislation and regulatory frameworks, 2) leverage international partnerships to increase mutual reliance and worksharing, 3) reduce the regulatory burden on the health product industry, 4) enhance transparency and openness by making relevant, timely and useful information available to the public, and 5) enhance our ability to respond to emerging risks.

These priorities are integrated into each Program's workplans and activities for 2014-2015. We are confident that by focussing on these priorities, our compliance and enforcement activities will have a positive impact on the safety of health products in Canada and ultimately the health of Canadians. We are proud of the professionalism and expertise of the Inspectorate team across the country, and, by working with our partners, we can achieve positive outcomes in support of Health Canada's mandate to improve the health and safety of Canadians.

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CONTENTS

EXECUTIVE SUMMARY

Mandate

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 (CTO).

This mandate is achieved through a number of core activities such as: inspections, complaint follow-up activities including recalls, incidents, public advisories, compliance verifications and investigations, border integrity activities, and laboratory analyses. 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 on this mandate through the Health Products and Food Branch (HPFB) Inspectorate and the Regions and Programs Bureau (RAPB).

Licensing and Inspection Programs

In Canada, drug establishments that fabricate, package, label, distribute, import, wholesale, or test a drug must hold a drug establishment licence (DEL). Medical device establishments that import or sell medical devices must hold a medical device establishment licence (MDEL) and blood operators must also hold a licence while CTO establishments, including source establishments, establishments that distribute within Canada, and establishments that import for further distribution must hold a registration. Donor semen processors and importers must give Health Canada advance notice of their activities. Clinical trials need to be authorised through the issuance of a No Objection Letter (NOL) by Health Canada.

The Inspectorate has regularly scheduled/cyclical inspection programs for drug good manufacturing practices (GMP), medical devices, blood, semen, cells, tissues and organ establishments. The frequency of these inspections is based on the type of facility and the activity being conducted. Additional inspections are also carried out as required to assess compliance. The Inspectorate also conducts inspections to ensure compliance to good pharmacovigilance practices (GVP) and good clinical practices (GCP). The inspections for these programs are based on the level of risk and resources available since they do not have a predetermined inspection cycle.

Specific inspection procedures vary across product lines according to their associated Regulations. However, all inspection procedures conform to the requirements of the Inspectorate's Quality Management System. To further enhance uniformity of inspection approach across product lines, the Inspectorate's National Training Unit coordinates training to ensure Inspectorate staff acquire and maintain the knowledge, skills, and competencies they need to professionally deliver Canada's National Compliance and Enforcement Program.

Domestic Inspection Approach

During an inspection, the inspector assesses the activities conducted by the regulated establishment and records all deviations against a regulatory requirement as observations. Observations are classified as critical (Risk 1), major (Risk 2), or minor (Risk 3) depending on the risk of harm to the consumer or the risk of compromising the integrity of the health product. Based on the number and types of observations made during an inspection as well as the class of product, the establishment's activities are issued a rating which deems them to be compliant (C) or non-compliant (NC) with the *Food and Drugs Act* and its associated Regulations. In either case, all observations are addressed by the regulated party through a Corrective Action/ Preventative Action plan.

Receiving an NC rating could result in various actions including but not limited to a proposal to suspend a licence, an amendment with terms and conditions, a shortened inspection cycle, additional reporting requirements or a cancellation of registration, depending on the product. Identified deficiencies in product quality could also result in product recalls and advisories to notify Canadians of any potential health risks.

Foreign Inspection Approach

Given the global nature of drug manufacturing, not all drug products available in Canada are manufactured in Canada. Most foreign sites are inspected by trusted regulatory partners. However, Health Canada can choose to inspect a foreign drug manufacturing site depending on several risk criteria. Coordinating foreign site inspections with regulatory partners is an example of how Health Canada is leveraging international partnerships with foreign regulatory bodies to increase worksharing.

In 2013-2014, the Inspectorate conducted 13 drug foreign on-site inspections, 1,275 drug foreign site paper reviews, operationalized a new Mutual Recognition Agreement (MRA) to exchange Certificates of Compliance with Slovenia, and expanded the MRA with the United Kingdom to include veterinary drugs. It was also the first year that Health Canada expanded its medical device inspection program to include foreign establishments; there were 68 paper-based foreign medical device inspections conducted in 2013-2014.

2013-2014 Inspection Statistics - Highlights

This report outlines inspection activities conducted by the Inspectorate in FY 2013-2014. Inspection results are summarized by product line and inspection type, and are explained according to relevant regulatory requirements. Examples of observations illustrating the most frequently cited sections of the applicable Regulations are given for each inspection program.

In 2013-2014, Health Canada conducted 1,238 domestic on-site inspections, made thousands of observations requiring corrective actions, and issued 30 domestic NC ratings. For establishments that received a NC rating, Health Canada has taken appropriate enforcement actions. The data presented in this report are based on a point in time; numbers may vary slightly depending on timing of data retrieval and ongoing activities.

Blood Inspections

- A total of 38 inspections were conducted for which 157 observations were noted. All establishments inspected were found to be in compliance (100% compliance rate) at the time of the inspection.
- The key priority in FY 2014-2015 is to support the implementation of the *Blood Regulations* which will come into force on October 23, 2014.

Cells, Tissues and Organs (CTO) Inspections

- A total of 53 inspections were conducted for which 304 observations were noted. All establishments inspected were found to be in compliance (100% compliance rate) at the time of the inspection.
- The key priority in FY 2014-2015 is to continue monitoring the compliance of CTO establishments with the *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* (CTO Regulations).

Drug Good Clinical Practices (GCP) Inspections

- A total of 61 clinical trial site inspections were conducted for which 553 observations were noted. The compliance rate was 92% with 5 sites receiving a NC rating.
- Key priorities in FY 2014-2015 are to evaluate site selection procedures and build the capacity of the GCP program through cross-training inspectors.

Drug Good Manufacturing Practices (GMP) Inspections

- A total of 428 domestic and 13 foreign on-site drug GMP inspections were conducted for which 2,933 observations were noted. The compliance rate was 96%, with 19 domestic NC ratings issued.
- Key priorities in FY 2014-2015 are to develop and implement the API (Active Pharmaceutical Ingredient) program and apply process efficiencies.

Good Pharmacovigilance Practices (GVP) Inspections

- A total of 86 establishments were inspected for which 268 observations were noted. The compliance rate was 99% with only 1 site receiving a NC rating.
- Key priorities in FY 2014-2015 are to further develop a non-compliance response strategy and move toward a risk-based approach for GVP inspections.

Medical Devices Inspections

- A total of 539 inspections were conducted for which 3,213 observations were noted. The compliance rate was 99% with 7 sites receiving a NC rating.
- Key priorities in FY 2014-2015 are to integrate paper-based foreign inspections into the inspection program, link non-compliances and licence suspensions and enhance stakeholder partnerships.

Semen Inspections

- A total of 33 inspections were conducted for which 8 observations were noted. All establishments inspected were found to be in compliance (100% compliance rate) at the time of the inspection.
- A key priority in FY 2014-2015 is to continue monitoring the compliance of donor semen processors, importers and distributors with the *Processing and Distribution of Semen for Assisted Conception Regulations* (Semen Regulations).

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 six licensable activities: fabricate, test, package/label, distribute, wholesale and import. As of October 23, 2014, human blood and blood components intended for transfusion or further manufacturing into human drugs will be regulated under the *Blood Regulations*.

In FY 2013-2014, there were 3 blood operators with 53 buildings/sites across Canada. Every building/site in which a blood operator proposes to conduct licensable activities is required to be licensed 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). Main centres are inspected annually, sub-centres are inspected every 2 years and fixed sites are inspected every 3 years. 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.

Inspection Results and Statistics

In FY 2013-2014, a total of 38 inspections were conducted. All establishments were found to be in compliance with the Regulations at the time of the inspection.

Regulatory Sections Cited most Frequently

A total of 157 observations were noted during the 38 inspections conducted in FY 2013-2014. ***Figure 1.1*** illustrates the prevalence of observations associated with the different sections of the Regulations. The majority of observations were cited against C.02.012 Manufacturing Control, C.02.020 Records and C.02.005 Equipment. Examples of these observations are listed in ***Table 1.1***.

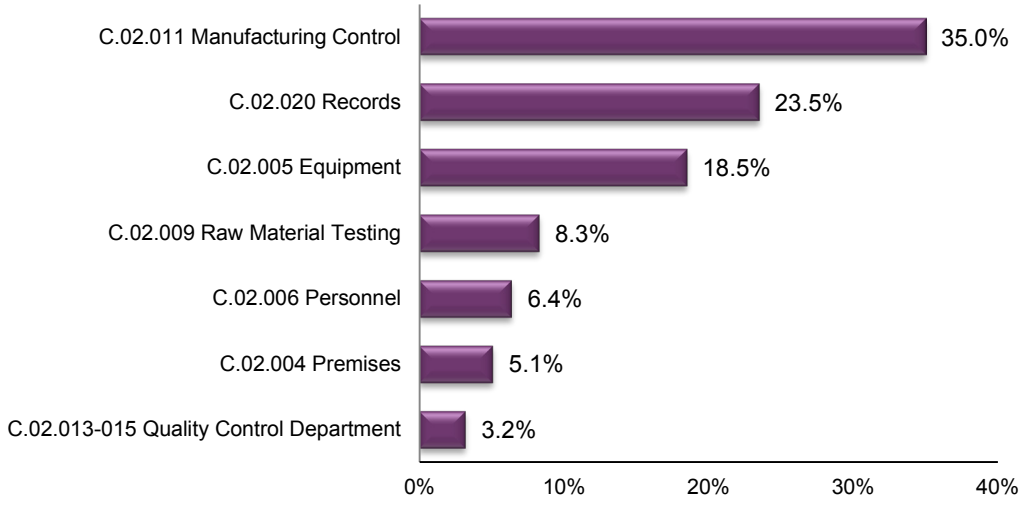

Figure 1.1 Sections of the *Food and Drug Regulations* most frequently cited as a percentage of the total number of observations cited during inspections conducted nationally. (FY: April 1, 2013 – March 31, 2014)

TABLE 1.1
Examples of observations from frequently cited sections of the *Food and Drug Regulations* - Blood Inspections

C.02.012 Manufacturing Control	• During the observation of phlebotomy for collection of whole blood units, the collection containers were not removed from the shakers and mixed manually on a consistent basis. This is contrary to step X of SOP XYZ. • Some documents used locally in X location only were listed as "in use at Y location" in the Controlled Document Index. • A rescinded form was being used while conducting quality inspections of critical supplies.
C.02.020 Records	• There was no documented process to verify the functionality of the archived electronic records (including donor suitability results) in the event of changes to computer equipment or its programs. • The 2012 and 2013 testing files retained by the quality assurance department were incomplete in that the files did not include the test data as required by SOP X. • The "Premises Monthly Inspection" reports for March, October and November 2012 were not maintained. • An outdated (2008) version of a form was used to record adverse transfusion reactions received in 2013.
C.02.005 Equipment	• The Equipment X Maintenance Log (Daily/Monthly) for the month of February 2013 could not be located during the inspection. • The Preventive Maintenance (PM) stickers on Equipment Y were not consistently completed. • The probe was labelled as PROBE-A, but the chart recorder was labelled as PROBE-B. • The digital clock had not been assigned an equipment identification number and was not currently subject to a preventive maintenance schedule.

Risk Ratings of Observations

A total of 157 observations were noted. The majority of these observations were assigned a Risk 3 rating (88%) and the remaining observations were assigned a Risk 2 rating (12%) as shown in ***Figure 1.2***. No Risk 1 observations were noted.

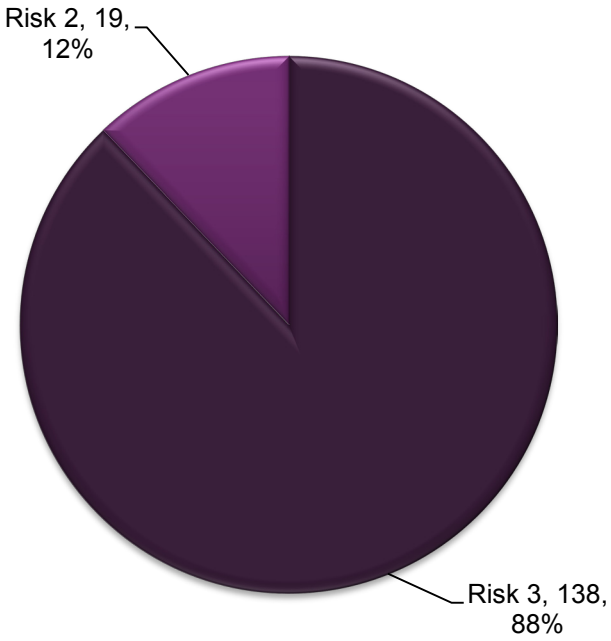

Figure 1.2 Distribution of risk ratings of observations during inspections conducted nationally. (FY: April 1, 2013 – March 31, 2014)

Forward Planning: FY 2014-2015 Key Priorities

The key priority for the blood inspection program is to support the implementation of the new *Blood Regulations* including: 1) finalizing and posting quality documents on the Health Canada website, 2) developing compliance promotion materials and a Frequently Asked Questions (FAQ) document for stakeholders, and 3) assessing the compliance of blood establishments with the *Blood Regulations*.

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

Background

In Canada, organs and minimally manipulated cells and tissues are regulated under the *Food and Drugs Act* (Act) and the *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* (CTO Regulations).

The purpose of the CTO Regulations is to minimize potential health risks to recipients of human cells, tissues and organs for transplantation. 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.

As of March 31, 2014, 108 Canadian CTO establishments were 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 consistency in statistical analysis and reporting, all data presented in this report are based on 138 registered Canadian CTO programs.

The frequency with which CTO inspections are conducted is outlined in the *Inspection Strategy for Cells, Tissues and Organs Establishments* (POL-0057). Inspection frequency is based on the risk of the activity and the overall ratings of the last two inspections.

Inspection Results and Statistics

A total of 53 of the 138 registered Canadian CTO programs were inspected. All programs inspected were found to be in compliance at the time of the inspection. ***Figure 2.1*** shows the national distribution of the 10 types of domestic CTO programs registered with Health Canada.

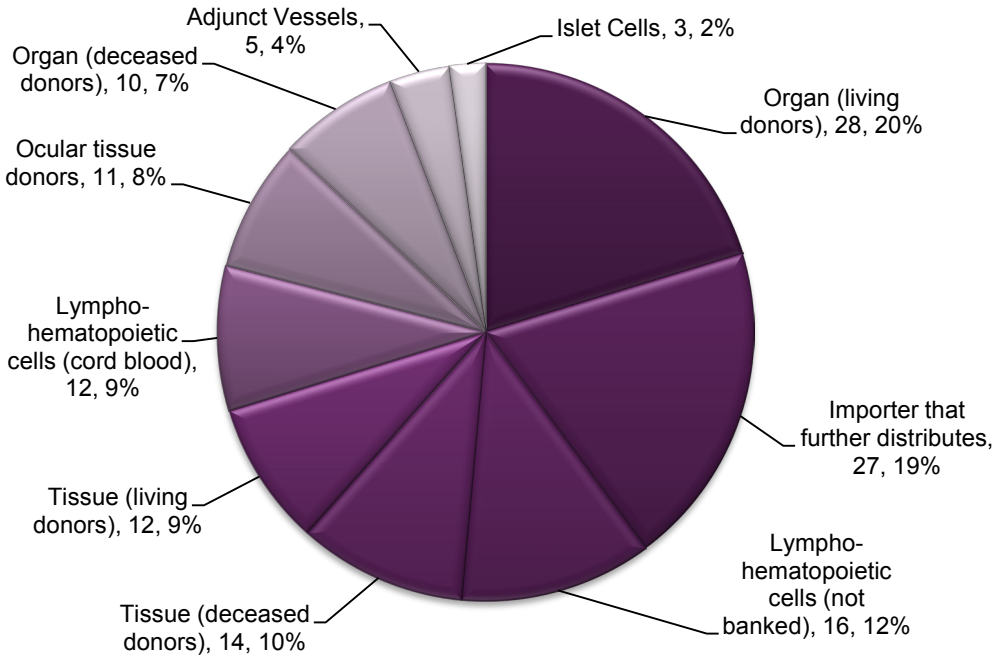

Figure 2.1 The national distribution of the ten types of registered Canadian CTO programs. (FY: April 1, 2013 – March 31, 2014)

Regulatory Sections Cited most Frequently

A total of 304 observations were noted during the 53 inspections. ***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) and donor suitability assessment (sections 18-23). Examples of these observations are listed in ***Table 2.1***.

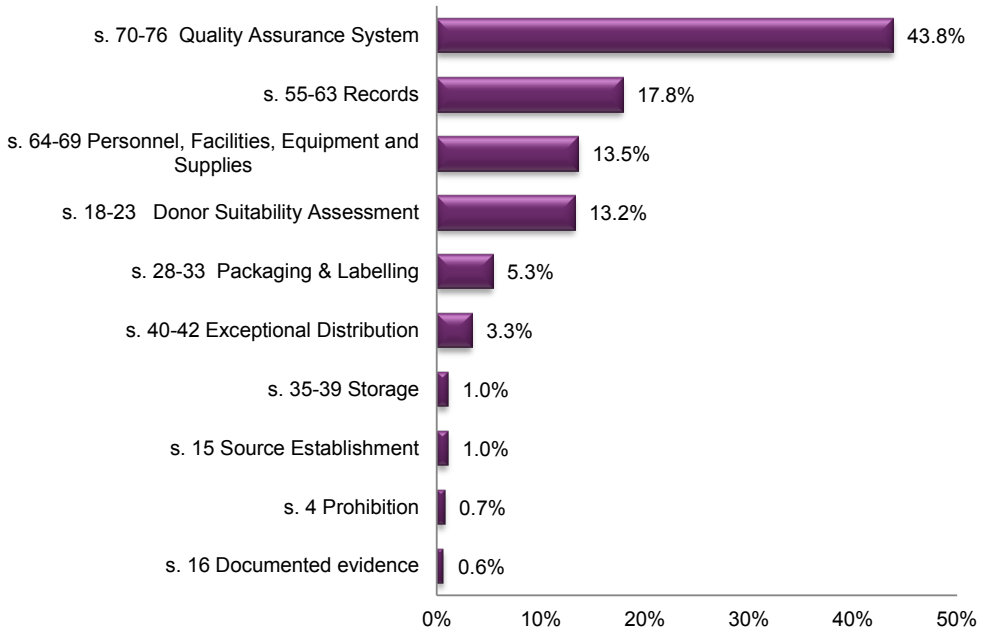

Figure 2.2 The top ten sections of the *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* (CTO Regulations) most frequently cited as a percentage of the total number of observations cited during inspections conducted nationally. (FY: April 1, 2013 – March 31, 2014)

TABLE 2.1
Examples of observations from frequently cited sections of the *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* (CTO Regulations) - Cells, Tissues, Organs Inspections

s. 70-76 Quality Assurance System	• The establishment's standard operating procedures did not always meet all the requirements of the *Safety of Human Cells, Tissues and Organs for Transplantation Regulations*. • There was no SOP specifying all the maintenance requirements of Equipment X. • There was no standard operating procedure for the audit of applicable activities carried out by the establishment. • There was no system in place to ensure all procedures were kept up to date.

s. 55-63 Records	• Records kept by the establishment were not always accurate and complete.
	  • The time section on the Identifier Sheet for Donor X was not completed.
	  • The Notice of Exceptional Distribution for kidney donor X did not contain the Transplant Medical Director's signature, time and date.

s. 64-69 Personnel, Facilities, Equipment and Supplies	• Preventative maintenance of a freezer used to store tissue was not always performed quarterly. • The critical supply area temperature was not monitored to ensure that the specific storage conditions of the critical supplies were met. • There was no documentation to demonstrate that initial and ongoing training was performed for new and revised SOPs.

Risk Ratings of Observations

A total of 304 observations were noted and risk rated. The majority of these observations were assigned a Risk 3 rating (88.2%), then a Risk 2 rating (11.5%) as shown in ***Figure 2.3***. One Risk 1 observation was noted (0.3%) against Section 4 of the CTO Regulations.

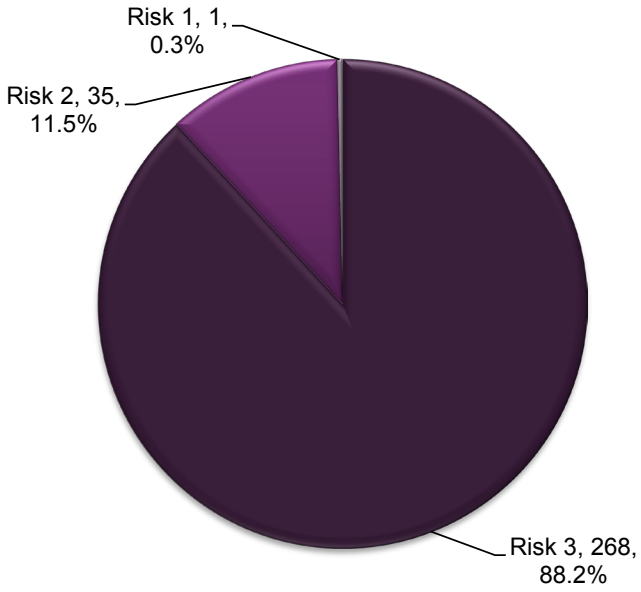

Figure 2.3 Distribution of risk ratings of observations during inspections conducted nationally. (FY: April 1, 2013 – March 31, 2014)

Forward Planning: FY 2014-2015 Key Priorities

The key priority for the CTO program for FY 2014-2015 is to continue monitoring the compliance of CTO establishments with the CTO Regulations and taking compliance and enforcement actions as appropriate.

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. 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).

In FY 2013-2014, Health Canada inspected 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 data collected in clinical trials. 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). Site selection for inspection is based on risk and applies to all on-going Phase 1 to 4 and closed clinical trials in Canada.

Inspection Results and Statistics

During the period covered in this report, 61 clinical trial sites were inspected, 56 of which received a C rating. Studies conducted at these sites involved biological, pharmaceutical, and narcotic/controlled investigational drugs. In the cases where an NC rating was assigned, the Inspectorate took action as per its regular process, including requiring the inspected parties to immediately correct the deficiencies identified, and recommending to the Health Canada directorate that issued the authorization that the authorization to conduct the study be suspended or cancelled.

Regulatory Sections Cited most Frequently

A total of 553 observations were noted during the inspection of 61 clinical trial sites. Of the 553 observations cited, all were against Division 5 of Part C. The majority of these observations were cited against requirements for Systems and Procedures C.05.010 (c), Records C.05.012 and Training C.05.010 (g) as shown in ***Figure 3.1***. Examples of these observations are listed in ***Table 3.1***.

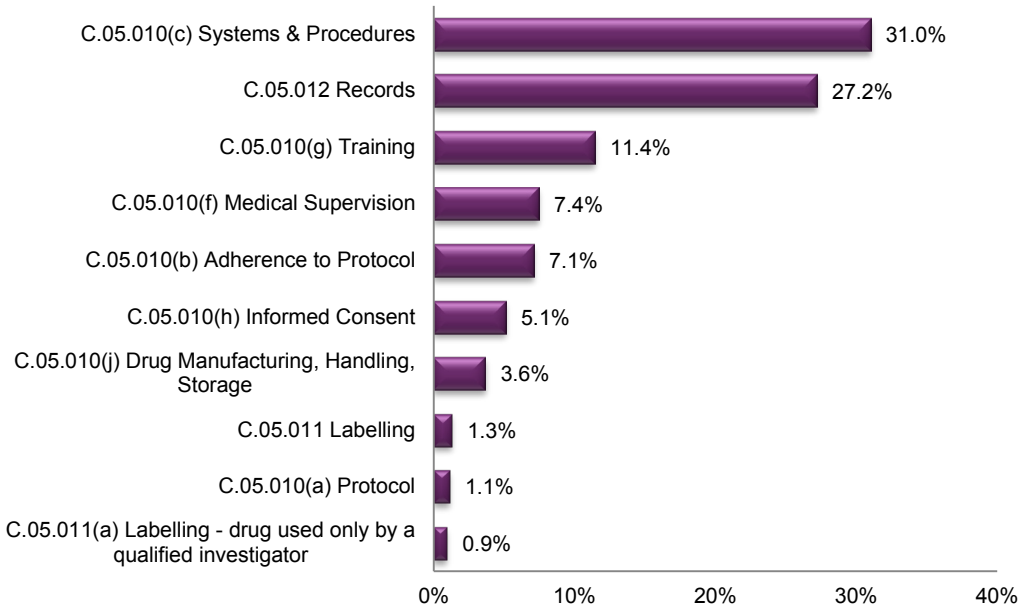

Figure 3.1 Sections of the Division 5 of Part C of the *Food and Drug Regulations* most frequently cited as a percentage of the total number of observations cited during inspections conducted nationally. (FY: April 1, 2013 – March 31, 2014)

TABLE 3.1
Examples of observations from frequently cited sections of the *Food and Drug Regulations* - Good Clinical Practices Inspections

C.05.010(c) Systems and Procedures	• There was no procedure in place for the calibration of the scale used to measure subject weight, which was an inclusion criterion. • Access to the systems used to store subject files during the conduct of the trial was not removed at the end of the employment of the study coordinator.
C.05.012 Records	• Data reported in the case record form (CRF) were not always consistent with the source documents. • Drug accountability records were not complete for the investigational drug in the study. • There was no documentation demonstrating that electronic systems were validated against a recognized system.
C.05.010(g) Training	• A nurse practitioner had been delegated the task of 'pre-screening.' However, there was no documented evidence that she had been trained on the protocol. • There was no documented evidence to show that staff involved in the trial were trained on Division 5 of the *Food and Drugs Regulations* (FDR) or ICH E6: GCP. • According to the list of delegation of responsibilities, the duties assigned to the research coordinator were the same as those assigned to a registered nurse. However, there were no qualifications on file for the research coordinator to support the conduct of those duties. • The training on how to report Serious Adverse Event (SAE) was not sufficient.
C.05.010 (f) Medical Supervision	• Records of physical exams were not signed or initialed by the qualified investigator (QI), and there is no indication that he/she has reviewed medical history and vital signs to confirm that the subject could be included in the trial. • The QI was not readily available to study subjects during his/her prolonged absence and there was no medical oversight coverage during these absences.

Risk Ratings of Observations

A total of 553 observations were noted. Of the observations noted, 278 were rated a Risk 2 (50%), 263 were rated a Risk 3 (48%), and 12 were rated a Risk 1 (2%) as shown in ***Figure 3.2***. All observations were associated with Division 5 of Part C of the *Food and Drug Regulations*. All Risk 1 observations were cited with respect to Section C.05.010 (f) that requires that the sponsor must ensure, at each clinical trial site, that medical care and medical decisions are under the supervision of the qualified investigator.

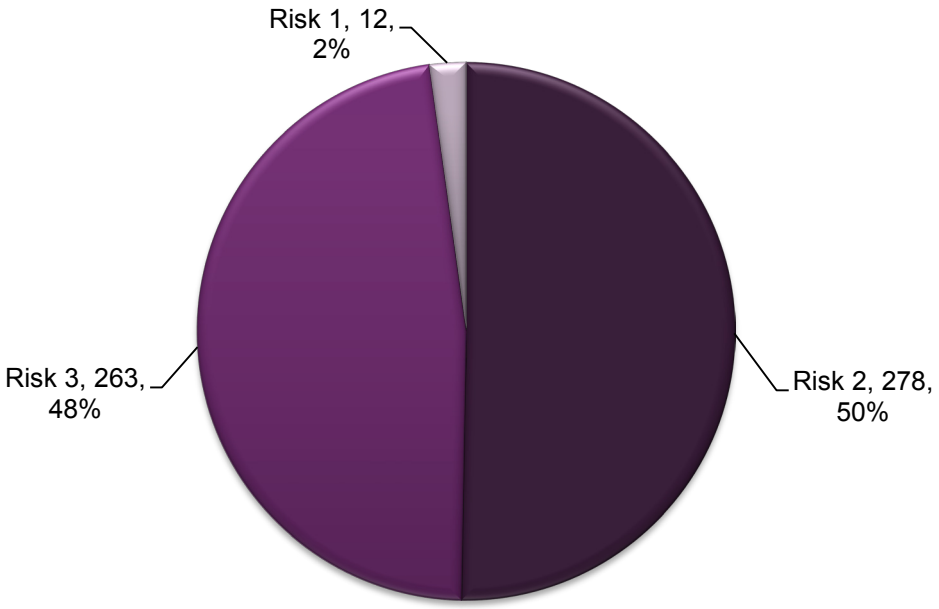

Figure 3.2 Distribution of risk ratings of observations during Good Clinical Practices inspections conducted nationally. (FY: April 1, 2013 – March 31, 2014)

Forward Planning: FY 2014-2015 Key Priorities

The key priorities for the GCP program will be: 1) evaluation of the enhanced site selection procedure, 2) completion and review of quality documents, and 3) continuous training and professional development of staff.

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) help ensure drugs are consistently produced and controlled to meet quality standards appropriate to their intended use.

In the FY 2013-2014 the Inspectorate was responsible for conducting inspections of establishments involved in the fabrication, packaging/labelling, testing, importation, distribution or wholesaling of the category of drugs listed in Table II of Section C.01A.008 of the *Food and Drug Regulations*. These inspections were conducted to verify the compliance with GMP requirements as outlined in the *Food and Drug Regulations*, which is a requirement for the issuance of an Establishment Licence.

The initial inspection of an establishment is triggered by the receipt of a Drug Establishment Licence Application. The Inspectorate endeavours to perform an initial on-site inspection within three months of the date of receipt of a complete Drug Establishment Licence Application. A regular inspection is then conducted within 12 months of the initial inspection. After that, the date of subsequent inspections 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.

Given the global nature of the drug manufacturing business, not all drug products available in Canada are manufactured in Canada. Mutual Recognition Agreements (MRA) are established based on the mutual evaluation of equivalency of regulatory frameworks. Once in place, the import of drugs from MRA countries is facilitated through the exchange of a Certificate of Compliance instead of a full paper review or on-site inspection. For non-MRA countries, to ensure the GMP compliance of foreign sites that fabricate, package/label or test drugs to be imported into Canada, Health Canada reviews the inspection reports of trusted regulatory partners. Where such inspections are not available for a foreign site, or upon the request of an importer, Health Canada may conduct an inspection. The decision to inspect a foreign site is based on several criteria such as the compliance history of the site, the nature of the drug products manufactured, the risk level of the activities taking place (e.g. sterile manufacturing), the location, the date of the last inspection and the overall risk assigned to the site, among other factors.

In FY 2013-2014, the Inspectorate conducted 1,275 drug foreign site paper reviews and 13 foreign site inspections. Also in the past year, the MRA with Slovenia was operationalised and the MRA with the United Kingdom was expanded to include veterinary drugs.

Inspection Results and Statistics

In FY 2013-2014, 428 Drug GMP inspections were conducted and 411 inspections resulted in the issuance of a compliant rating. Additionally, 13 foreign on-site drug GMP inspections were conducted, and 12 sites received a compliant rating.

One establishment may be licensed for multiple activities, thus the total number of actual establishments is not equal to the total number of licence holders depicted for each activity in ***Figure 4.1***.

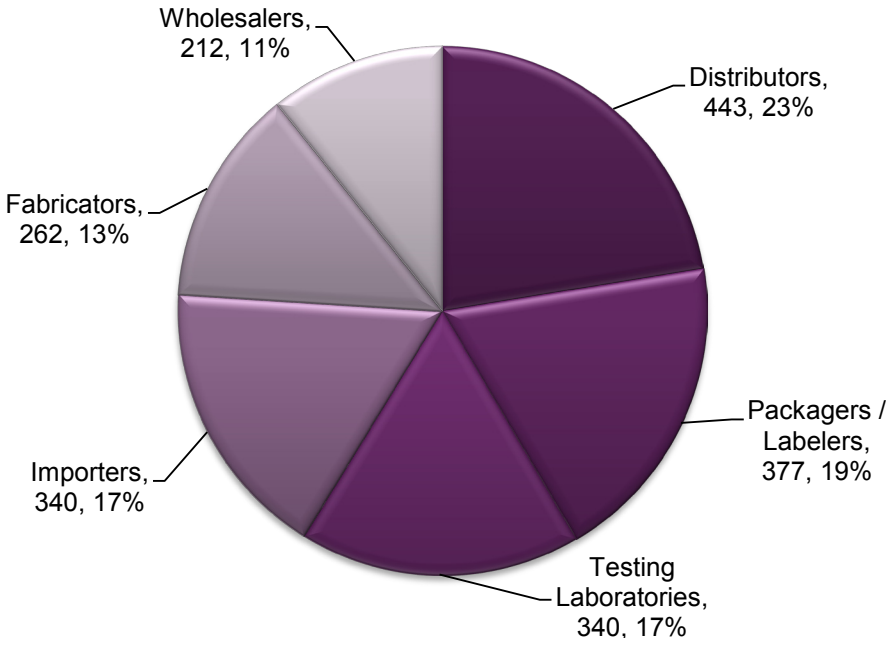

Figure 4.1 Proportion of Drug Establishment Licence (DEL) holders by activity. (FY: April 1, 2013 – March 31, 2014)

Regulatory Sections Cited most Frequently

A total of 2,933 observations were noted during the 428 inspections conducted in FY 2013-2014. The majority of observations were cited against requirements for the quality control department C.02.013-15, Manufacturing Control C.02.011-12, and Records C.02.020-24 as shown in ***Figure 4.2***. Examples of these observations are listed in ***Table 4.1***.

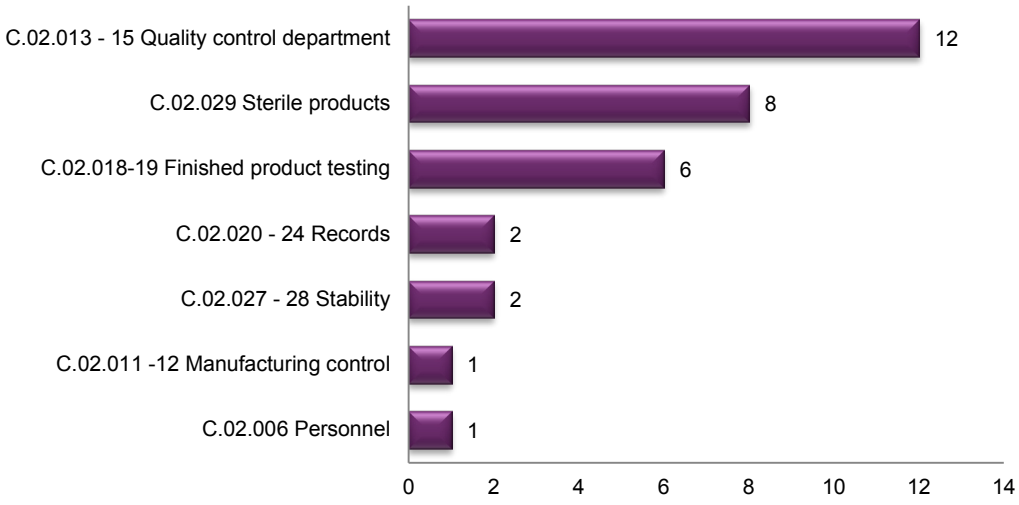

Figure 4.2 The top ten sections of the *Food and Drug Regulations* (FDR) most frequently cited as a percentage of the total number of observations cited during inspections conducted nationally. (FY: April 1, 2013 – March 31, 2014)

TABLE 4.1
Examples of observations from frequently cited sections of the *Food and Drug Regulations* - Good Manufacturing Practices Inspections

C.02.013 - 15 Quality control department	• Not all the Batch Release Notes and Batch Release Checklists were filled out and signed by the quality control department. • A change control procedure had not been established. • During the release of a lot, the firm had not received or reviewed the Certificate of Analysis prepared by the manufacturer. • During the temperature verification of the shipping of drug products, the firm was not recording the location the drug products were shipped to or what calibrated temperature monitoring device had been used for this activity.
C.02.011 - 12 Manufacturing control	• Manufacturing operations are not performed in such a way as to prevent cross-contamination of products. • Temperature mapping and temperature monitoring of the warehouse was not performed. • Quality Agreement between the Company A and Company B did not include requirements to notify Company A of any rework, reprocessing and deviations. • The water system sampling and testing program was deficient.
C.02.020 - 24 Records	• The record retention timeframes stated in the written procedure were not in compliance with GMP requirements outlined in C.02.021, C.02.022 and C.02.023. • Not all the master production documents for product A were available on the premises. • There is no written procedure on proper documentation practices and no evidence that personnel are trained in documentation practices. • Proper documentation practices were not being used in the Cleaning Log (i.e. Dates were observed to be scratched out in the Cleaning Log, rather than crossed out and initialed).

Risk Ratings of Observations

During the 428 inspections 2,933 observations were noted. The majority of these observations were assigned a Risk 3 and 2 rating (50% and 49%, respectively), with the remaining observations being Risk 1 (1%) as shown in ***Figure 4.3***.

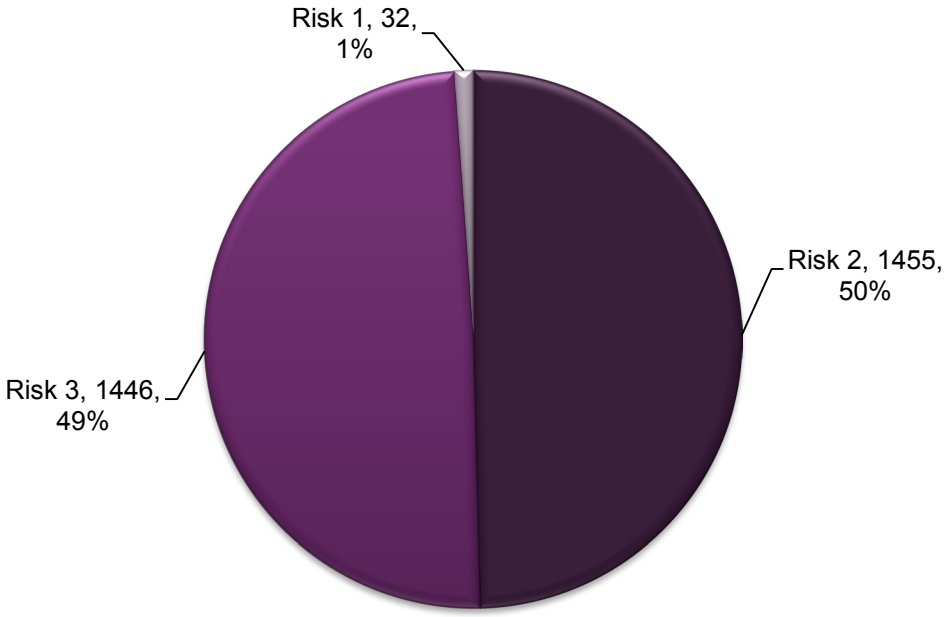

Figure 4.3 Distribution of risk ratings of observations during Good Manufacturing Practices inspections conducted nationally. (FY: April 1, 2013 – March 31, 2014)

Of the 32 Risk 1 observations, the highest number were recorded under C.02.013-15 Quality Control (12), followed by C.02.029 Sterile Products (8) as shown in ***Figure 4.4***. Given the high risk associated with the potential contamination of sterile products, this is generally the regulation most frequently attributed a Risk 1 rating (See the *2006-2011 Summary Report of the Drug Good Manufacturing Practices (GMP) Inspection Program* and the *2012-2013 Annual Inspection Summary Report*).

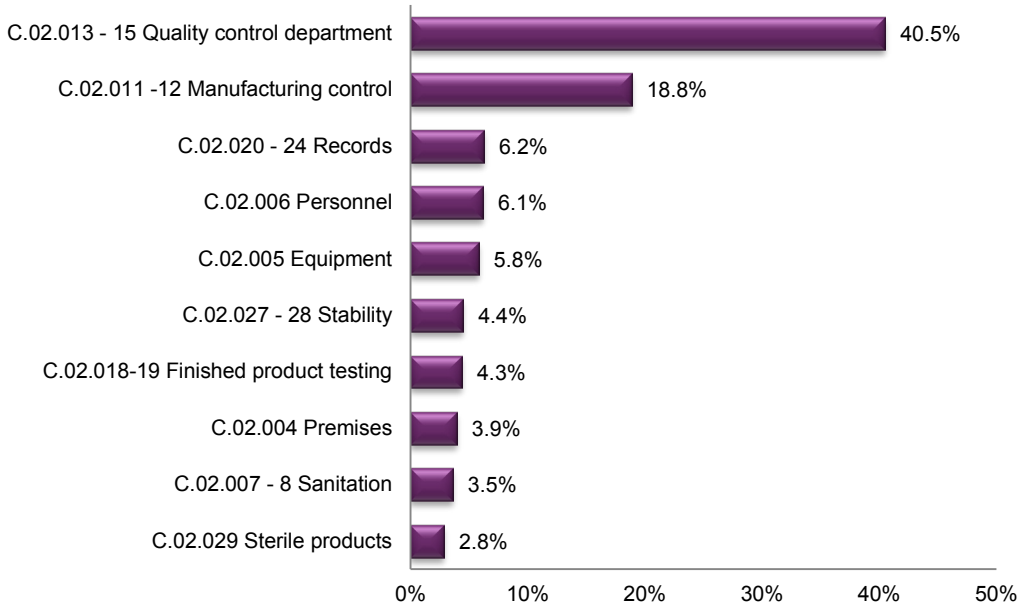

Figure 4.4 Sections of the *Food and Drug Regulations* (FDR) cited as Risk 1 observations during inspections conducted nationally. (FY: April 1, 2013 – March 31, 2014)

Forward Planning: FY 2014-2015 Key Priorities

The future vision for the GMP program is to continue to apply the risk-based approach to all GMP activities. As such, key priorities are focussed on achieving efficiencies in program review, processes, structure and stakeholder engagement. The key priorities for the GMP program will be: 1) enhancing the risk management process by developing tools to achieve operational efficiencies in managing and responding to emerging risk issues to create predictability and consistency, 2) collaborating with international partners to increase mutual reliance (i.e. MRA, Pharmaceutical Inspection Cooperation/ Scheme [PIC/S], RCC [Regulatory Cooperation Council] and RCI [Regulatory Cooperation Initiative]), 3) continued development and implementation of a new business model for reviewing foreign site GMP evidence, and 4) Data analysis to develop a risk-based strategy for the Active Pharmaceutical Ingredient (API) inspection program.

CHAPTER 5
DRUG GOOD PHARMACOVIGILANCE PRACTICES (GVP) INSPECTION PROGRAM

Background

The purpose of the GVP inspection program is 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 a drug. These regulations are enforced to verify that manufacturers have and maintain a rigorous ADR management program. The continuous application of Good Pharmacovigilance Practices helps to ensure that marketed health products remain safe and effective after 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 ADRs from other companies or consumers. The following health products 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.

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.

The selection of establishments for GVP inspection is based on a variety of criteria including the compliance history of the establishment, information about the health product and reported adverse drug reactions. The duration of these inspections varies depending on the type of activities, the number of health products, and the volume of reported ADRs.

Inspection Results and Statistics

In FY 2013-2014, 86 inspections were conducted and 85 establishments were found to be in compliance at the time of inspection.

Regulatory Sections Cited most Frequently

A total of 268 observations were noted during the 86 inspections. As per ***Figure 5.1***, the top three sections of the *Food and Drug Regulations* against which observations were noted are C.01.017 Serious Adverse Drug Reaction Reporting, C.01.018 Annual Summary Report and Case Reports, and C.01.020 Maintenance of Records. Examples of these observations are listed in ***Table 5.1***.

Of note, only a small number of observations were cited under C.08.008(c) Efficacy, which is to be expected given the fact that not all establishments inspected produced new drugs. If a Notice of Compliance (NOC) is issued for a drug, then that drug is considered to be a 'new drug', regardless of how long it has been on the market. Section C.08.008(c) of the *Food and Drug Regulations* sets out requirements to report unusual failure in efficacy for new drugs only. 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.

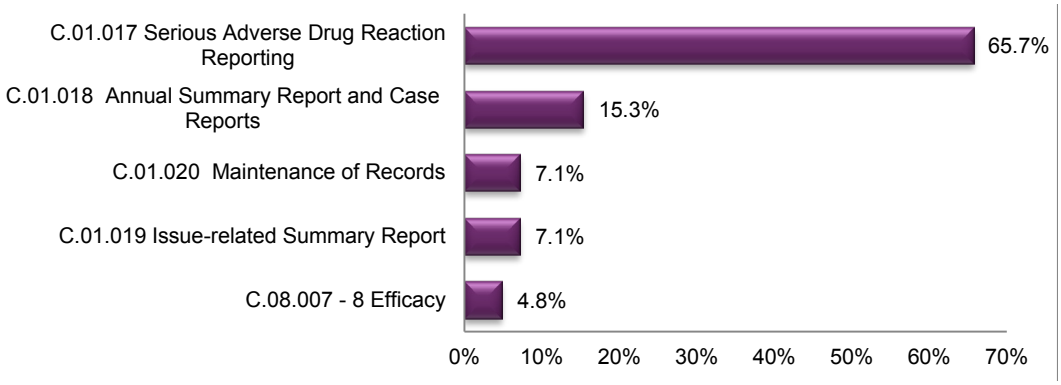

Figure 5.1 Sections of the *Food and Drug Regulations* most frequently cited as a percentage of the total number of observations cited during inspections conducted nationally. (FY: April 1, 2013 – March 31, 2014)

TABLE 5.1
Examples of observations from frequently cited sections of the *Food and Drug Regulations* - Good Pharmacovigilance Practices Inspections

C.01.017 Serious Adverse Drug Reaction Reporting	• Suspected adverse drug reactions had not been recorded, tracked and/or logged appropriately. • The literature search section of the procedure does not provide sufficient detail regarding the current process used for conducting literature searches. • There is no adequate system in place for the receipt, handling, evaluation and reporting of Adverse Drug Reactions (ADRs). • There is no written procedure in place describing the process for conducting periodic self-inspections of Pharmacovigilance activities. • Lack of adequate contractual agreement in place to specify the processes by which an exchange of safety information, including timelines and regulatory reporting responsibilities, are taking place between the MAH and the third party responsible for pharmacovigilance.
C.01.018 Annual Summary Report and Case Reports	• There is no written procedure in place describing the process for preparing annual summary reports. • Annual summary reports were not always prepared on an annual basis for all drug products marketed in Canada as required by the *Food and Drug Regulations*.
C.01.020 Maintenance of Records	• There is no written procedure in place describing the process for the maintenance of adverse drug reaction records. • Documentation of follow-ups and/or follow-up attempts was not available for all adverse drug reaction reports.

Risk Ratings of Observations

A total of 268 observations were noted and risk rated. Of the observations noted, 144 were assigned a Risk 2 rating (54%) and 124 were assigned a Risk 3 rating (46%) as shown in ***Figure 5.2***. No Risk 1 observations were noted. Corrective actions proposed in response to the observations were found to be acceptable in all cases.

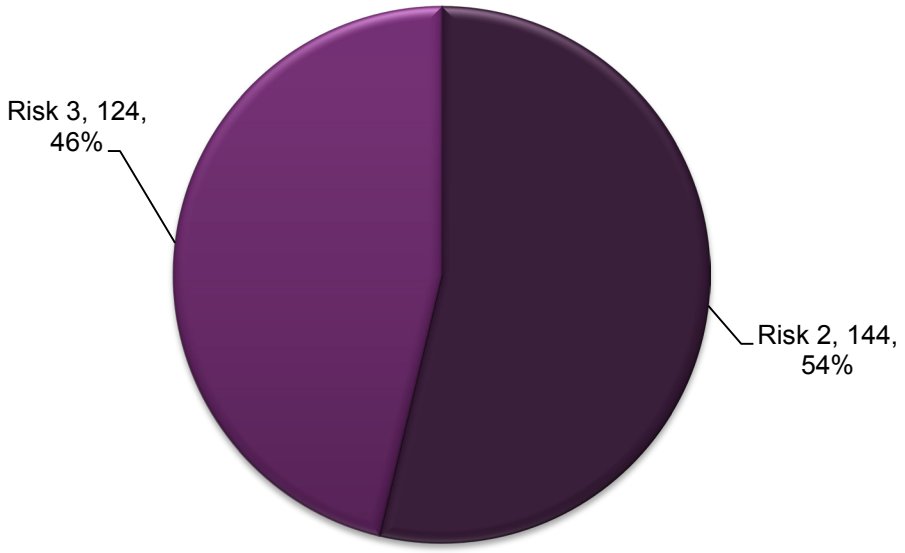

Figure 5.2 Distribution of risk ratings of observations during Good Pharmacovigilance Practices inspections conducted nationally. (FY: April 1, 2013 – March 31, 2014)

Forward Planning: FY 2014-2015 Key Priorities

The key priorities for the GVP program are: 1) the development of a non-compliance strategy for GVP inspections and 2) an assessment of the application of a risk-based approach to GVP inspections.

CHAPTER 6
MEDICAL DEVICES INSPECTION PROGRAM

Background

Health Canada's Inspectorate Program delivers a national compliance and enforcement program for medical devices, the authority for which is derived from the *Food and Drugs Act* (Act) and the *Medical Devices Regulations* (Regulations).

Companies conducting multiple activities are categorized by their highest risk activity. In addition, with respect to activities conducted by an establishment, distributing and importing are considered to be associated with a lower risk than manufacturing. For example, a company that manufactures and imports medical devices is categorized as a manufacturer. Inspection frequency for manufacturers is every 3 years, for importers is every 4 years and for distributors is every 5 years.

Inspection Results and Statistics

For FY 2013-2014, 539 inspections were conducted. A total of 532 establishments were found to be in compliance with the Regulations at the time of inspection.

As of April 2013, there were 2,406 domestic and foreign Medical Device Establishment Licence (MDEL) holders: 1,793 domestic and 613 foreign. The number of MDEL holders constantly fluctuates due to licence withdrawals/ cancellations, as well as the entry of new applicants into the market. ***Figure 6.1*** shows the proportion of licence holders identified as manufacturers, importers, and distributors. One establishment may be licensed for multiple activities, thus the total number of establishments nationally would not equal the total number of licence holders for each of the activities depicted in ***Figure 6.1***.

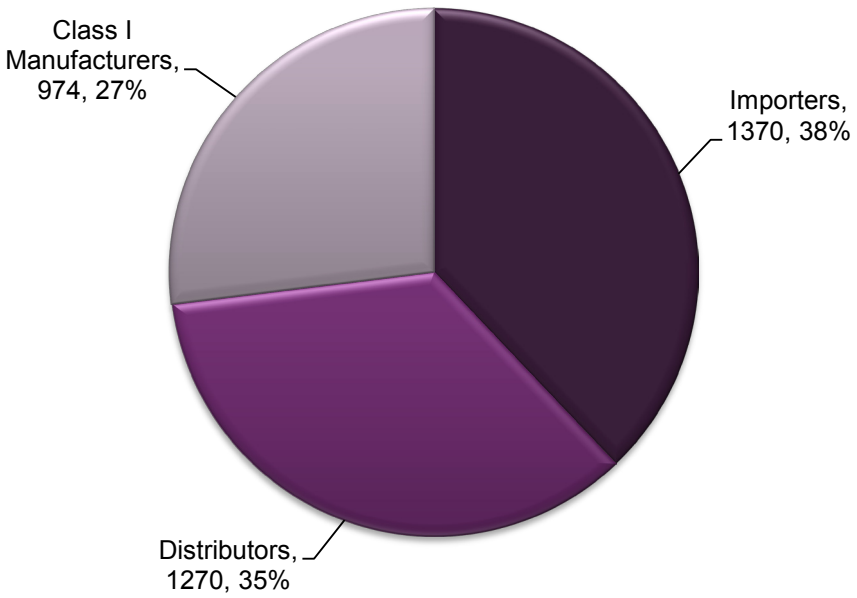

Figure 6.1 Proportion of Medical Device Establishment Licence (MDEL) holders who are identified as manufacturers, importers, and distributors (FY: April 1, 2013 – March 31, 2014)

Regulatory Sections Cited most Frequently

For FY 2013-2014, 539 inspections were conducted citing a total of 3,213 observations. Of these observations, over half (52.3%) were cited against four sections of the Regulations as shown in ***Figure 6.2***. Most observations were related to deficiencies in documentation relating to recall procedures (s. 58(b)), complaint handling and recalls (s.45 (g)), the investigation of complaints (s.58 (a)), and mandatory problem reporting (s. 45(h)). Examples of frequently cited observations are shown in ***Table 6.1***.

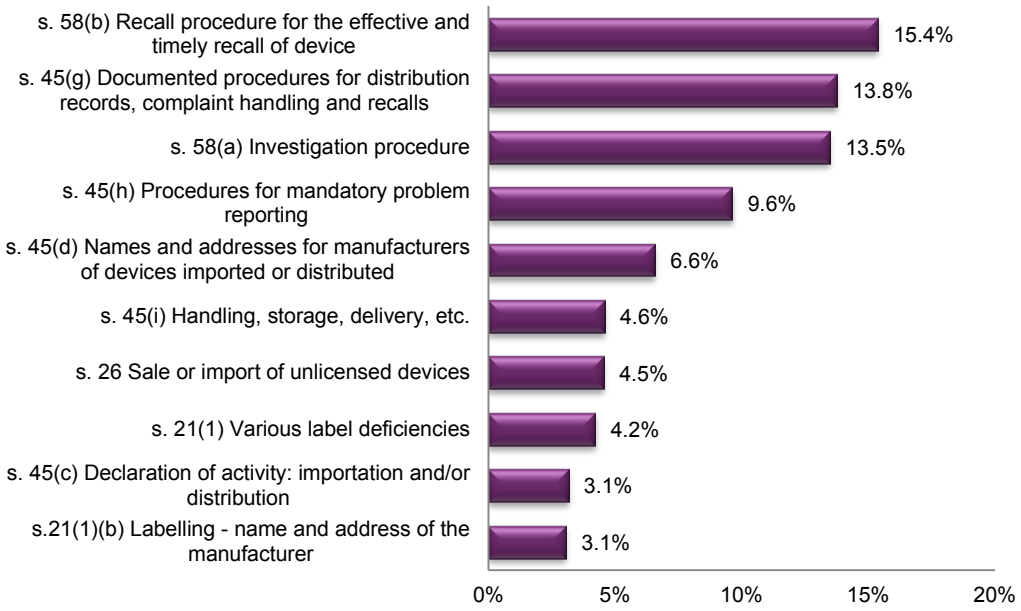

Figure 6.2 Sections of the *Medical Devices Regulations* most frequently cited as a percentage of the total number of observations cited during inspections conducted nationally. (FY: April 1, 2013 – March 31, 2014)

TABLE 6.1
Examples of observations from frequently cited sections of the *Medical Devices Regulations* - Medical Device Inspections

s. 58(b) Recall procedure for the effective and timely recall of device	• At the time of the inspection, the company did not have a designated quarantined area for recalled products. • The recall procedure was incomplete in that the procedure for sending recall preliminary and final reports to Health Canada was not specified. • The recall procedure was not adequate to assure that all recalls would be conducted in a timely and effective manner.
s. 45(g) Documented procedures for distribution records, complaint handling and recalls	• The company's procedure for distribution records does not meet the requirements of the following Regulations: s.55 Record retention s.56 Timely retrieval.
s. 58(a) Investigation procedure	• The company's procedure for complaint handling did not include timelines to ensure effective and timely investigation of the reported problems relating to the performance characteristics or safety of the device. • At the time of the inspection the company could not provide a documented procedure for complaint handling as attested to in the Medical Device Establishment application.

Risk Ratings of Observations

A total of 3,213 observations were noted during the 539 inspections. The majority of these observations were Risk 2 (62%) and Risk 3 (38%) with the remaining observations being Risk 1 (0.4%) as shown in ***Figure 6.3***.

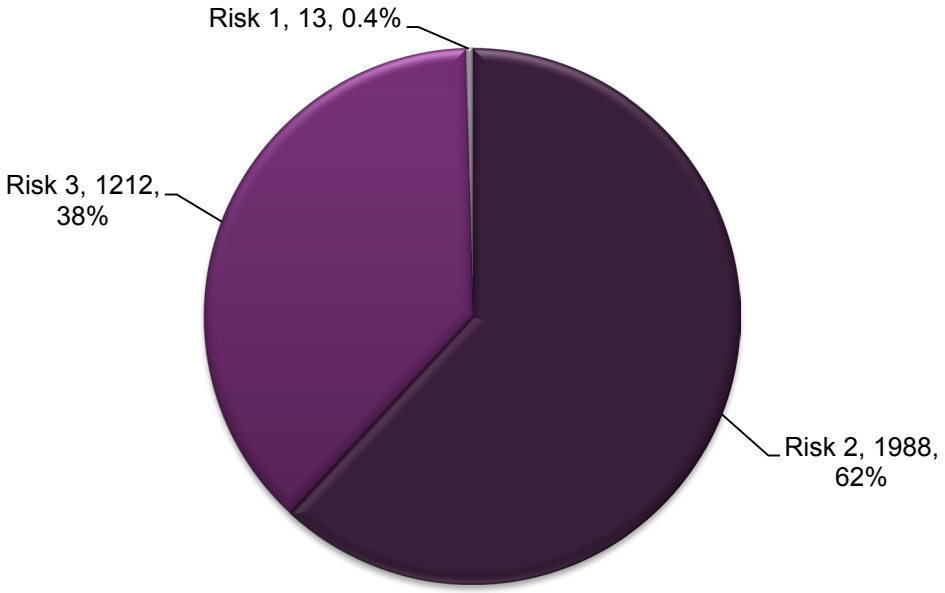

Figure 6.3 Distribution of risk ratings of observations during Medical Device Establishment inspections conducted nationally. (FY: April 1, 2013 – March 31, 2014)

The frequency of observations related to the sale or import of unlicensed devices (s.26) was 4.5%. This is significant because section of the Regulations accounted for the greatest number of Risk 1 observations as shown in ***Figure 6.4***. Deficiencies in documentation relating to recall procedures (s.58(2)) accounted for the second highest number of Risk 1 observations.

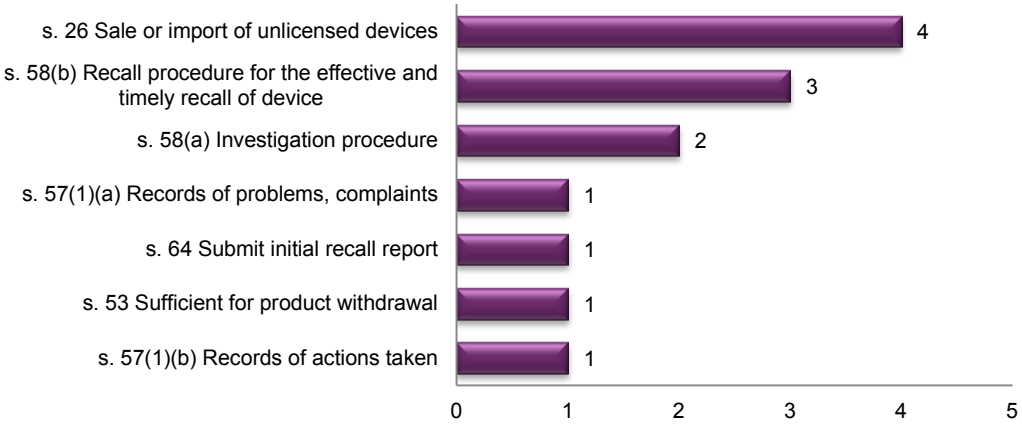

Figure 6.4 Sections of the *Medical Devices Regulations* or *Food and Drugs Act* cited as Risk 1 observations during inspections conducted nationally. (FY: April 1, 2013 – March 31, 2014)

Forward Planning: FY 2014-2015 Key Priorities

The key priorities for the Medical Devices Inspection program are: 1) to integrate paper-based foreign inspections into the inspection program, 2) to better understand the linkages between incidents of non-compliance and Medical Device Establishment Licence (MDEL) suspensions, and 3) to enhance partnerships with internal and external stakeholders.

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). Semen processors and importers are inspected annually, distributors that further distribute donor semen are inspected every 2 years and final distributors (including physicians) are inspected every 5 years. In addition, unannounced inspections may be considered 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.

Inspection Results and Statistics

During FY 2013-2014, 33 out of 115 active processors, importers and distributors of donor semen were inspected. All were found to be compliant with the Semen Regulations at the time of inspection.

In accordance with the Semen Regulations, processors and importers of donor semen must give 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 the Semen Regulations. ***Figure 7.1*** illustrates the total number of donor semen establishments in Canada.

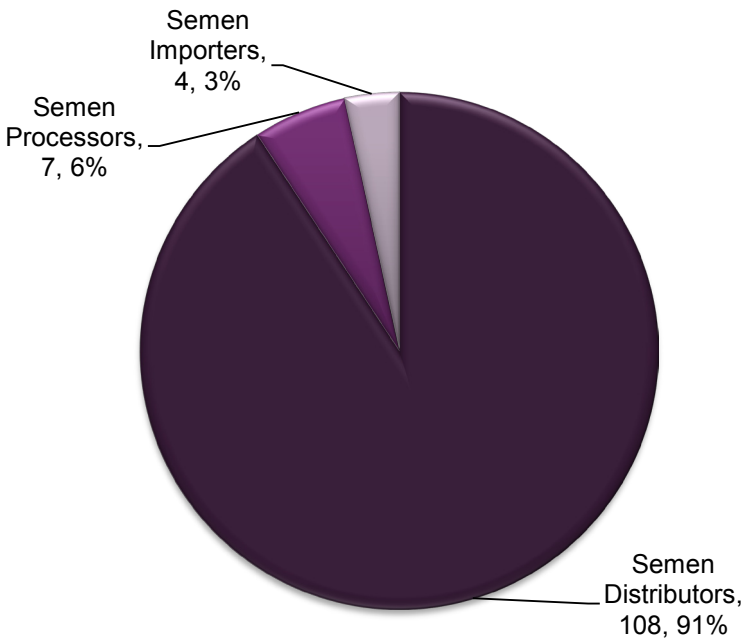

Figure 7.1 The national distribution of the three types of semen establishments. (FY: April 1, 2013 – March 31, 2014). Note: 3 semen processors and 1 semen importer were inactive during the period covered by this report.

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

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.

Regulatory Sections Cited most Frequently

During the 33 inspections, a total of 8 observations were noted. ***Figure 7.2*** illustrates the prevalence of observations associated with two sections of the Semen Regulations. Observations were cited against S.13 Distributor Records or against S.4-5 Prohibition-General Requirements. Examples of these observations are listed in ***Table 7.1***.

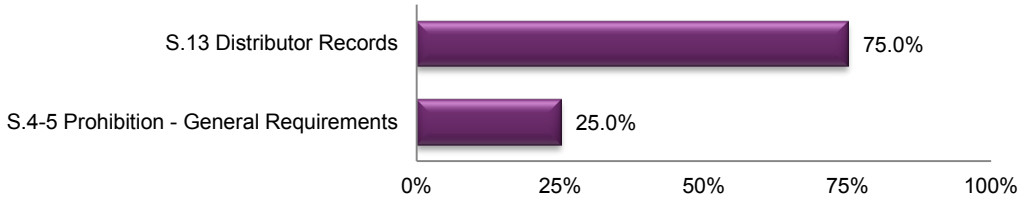

Figure 7.2 Sections of the *Processing and Distribution of Semen for Assisted Conception Regulations* (Semen Regulations) most frequently cited as a percentage of the total number of observations cited during inspections conducted nationally. (FY: April 1, 2013 – March 31, 2014)

TABLE 7.1
Examples of observations from frequently cited sections of the *Processing and Distribution of Semen for Assisted Conception Regulations* - Semen Establishment Inspections

S.13 Distributor Records	• For one of the files reviewed, there was no record of the patient's written consent to use donor semen for which special access had been granted.
S.4-5 Prohibition - General Requirements	• During work-up of a donor, the medical history questionnaire (Form XXXX, Rev.XX) for which the Medical Director review was completed, indicated an 'X' under 'Yes' for all the 38 conditions (i.e. metabolic/endocrine disease, muscular/bones/joint disease, and neurological disease including CJD) listed on page xx, yet there was no documentation to indicate follow-up. During the inspection, the foreign processor's correspondence indicated that the donor intended to answer 'No' to all the conditions as was the case on multiple subsequent medical history updates and that a note should have been made on the questionnaire clarifying the responses.

Risk Ratings of Observations

During the 33 inspections, a total of 8 observations were noted which were either Risk 3 (75%) or 2 (25%) as shown in ***Figure 7.3***. No Risk 1 observations were noted at the time of inspection.

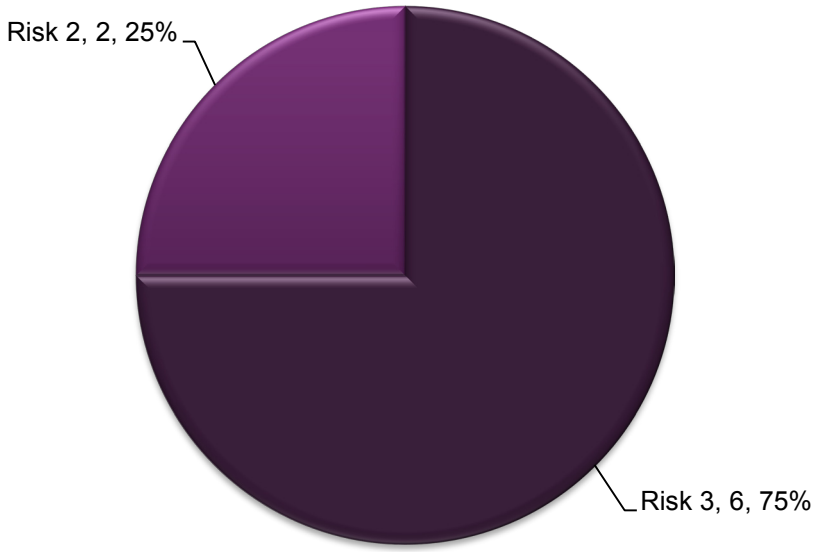

Figure 7.3 Distribution of risk ratings of observations during semen establishment inspections conducted nationally. (FY: April 1, 2013 – March 31, 2014)

Forward Planning: FY 2014-2015 Key Priorities

A key priority in FY 2014-2015 is to continue monitoring the compliance of donor semen processors, importers and distributors with the Semen Regulations and taking compliance and enforcement actions as appropriate.

DEFINITIONS

Compliant (C): At the time of 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 there are no observations or corrective actions required.

Critical observation (Risk 1): Observation of a critical deviation from the applicable regulations that describes a situation that may produce an immediate or latent health risk. Observations that involve fraud, misrepresentation or falsification of data are also considered critical.

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.

Major observation (Risk 2): Observation of a major deviation from the applicable regulations 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 the applicable Regulations.

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

Observation (Blood): A deviation from or deficiency in compliance 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. Observations are classified as Risk 1, Risk 2 or Risk 3 in accordance with the level of risk associated with the deficiency.

Observation (CTO): A deviation from or deficiency in compliance with the *Food and Drugs Act* or the *CTO Regulations* noted during the inspection of a cell, tissue or organ (CTO) establishment. Observations are classified as Risk 1, 2 or 3 in accordance with the level of risk associated with the deficiency.

Observation (Good Clinical Practices): A deviation from or deficiency in compliance with Division 5 of Part C of the *Food and Drug Regulations* noted during the inspection of a clinical trial. Observations are classified as Risk 1, 2 or 3 in accordance with the level of risk associated with the deficiency.

Observation (Good Manufacturing Practices): A deviation from or deficiency in compliance with Good Manufacturing Practices noted during the inspection of a drug establishment. Observations are classified as Risk 1, 2 or 3 in accordance with the level of risk associated with the deficiency.

Observation (Medical Devices): A deviation from or deficiency in compliance with the *Food and Drugs Act* or the *Medical Device Regulations* noted during the inspection of a medical device establishment. Observations are classified as Risk 1, 2 or 3 in accordance with the level of risk associated with the deficiency.

Observation (Good Pharmacovigilance Practices): A deviation from or deficiency in compliance with the *Food and Drug Regulations* pertaining to the reporting of adverse drug reactions or unusual failure in efficacy of new drugs noted during the inspection of a drug establishment. Observations are classified as Risk 1, 2 or 3 in accordance with the level of risk associated with the deficiency.

Observation (Semen): A deviation or deficiency to the *Food and Drugs Act* or the Semen Regulations noted during the inspection of a processor, importer or distributor of donor semen for assisted conception. Observations are classified as Risk 1, 2 or 3 in accordance with the level of risk associated with the deficiency.

REFERENCES

Chapter 1 Blood Inspection Program

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

Chapter 2 Cells, Tissues and Organs (CTO) Inspection Program

Food and Drugs Act
Safety of Human Cells, Tissues and Organs for Transplantation Regulations (CTO Regulations)
Compliance and Enforcement Policy (POL-0001)
Inspection Strategy for Cells, Tissues and Organs Establishments (POL-0057)
Guidance on Classification of Observations for Inspection of Cells, Tissues and Organs Establishments (GUI-0101)
Guidance Document for Cells, Tissues and Organs Establishments – Safety of Human Cells, Tissues and Organs for Transplantation

Chapter 3 Drug Good Clinical Practices Inspection Program

International Conference on Harmonization (ICH) Guidance, Topic E6 (ICH E6)
Inspection Strategy for Clinical Trials (POL-0030)
Annex 13 to the Current Edition of the Good Manufacturing Practices Guidelines – Drugs Used in Clinical Trials (GUI-0036)
Classification of Observations Made in the Conduct of Inspections of Clinical Trials (GUI-0043)
Guidance for Records Related to Clinical Trials (GUI-0068)

Chapter 4 Drug Good Manufacturing Practices Inspection Program

Compliance and Enforcement Policy (POL-0001)
Good Manufacturing Practices (GMP) and Establishment Licensing Enforcement Directive (POL-0004)
GMP Inspection Policy for Canadian Drug Establishments (POL-0011)
Good Manufacturing Practices (GMP) Guidelines – 2009 Edition (GUI-0001)
Risk Classification of Good Manufacturing Practices (GMP) Observations (GUI-0023)
Good Manufacturing Practices (GMP) for Active Pharmaceutical Ingredients (API) (GUI-0104)
Drug Establishment Good Manufacturing Practices – Pre-Application Package (Importers, Distributors and Wholesalers)
2006-2011 Summary Report of the Drug Good Manufacturing Practices (GMP) Inspection Program
2012-2013 Annual Inspection Summary Report

Chapter 5 Drug Good Pharmacovigilance Practices Inspection Program

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

Chapter 6 Medical Devices Inspection Program

Food and Drugs Act
Medical Devices Regulations
Guidance on the Medical Devices Inspection Program (GUI-0064)

Chapter 7 Semen Inspection Program

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