Health Canada Santé Canada

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

Health Products and Food Branch Inspectorate

Summary Report of Inspections of Cells, Tissues and Organs Establishments Conducted from August 2009 to June 2012

Date issued:
January 16, 2013

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

Canada

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Executive Summary

This document provides the result and analysis of cells, tissues and organs (CTO) program inspections conducted by Health Canada from August 2009 to June 2012. This is the first summary report issued since the inspection program was launched in August 2009. The objective of sharing inspection results, anonymously, is to increase awareness of compliance with Canadian regulatory requirements within the CTO community, while maintaining the confidentiality and privacy of those involved in the inspections.

The *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* (CTO Regulations) came into force on December 7, 2007, except for subsection 26 (1) , which came into force on June 7, 2008. The purpose of the CTO Regulations is to minimize the potential health risks to Canadian recipients of human CTO for transplantation.

In August 2009, Health Canada began inspecting registered Canadian CTO programs to facilitate compliance promotion and to assess their compliance with the CTO Regulations. During the 34 months covered in this report, a total of 125 out of 134 registered Canadian CTO programs have been inspected. Of the 9 registered CTO programs yet to be inspected, 5 are currently not-active and may not be inspected until they become active. The remaining 4 active CTO programs will be inspected by March 2013, and the results reported in the next summary report.

Of the 125 programs inspected, 108 (86 %) programs were assigned an overall compliant rating, and 17 (14%) programs were initially rated as non-compliant. Health Canada worked closely with the programs rated non-compliant to bring them into compliance. During the period covered in this report, Health Canada re-inspected 15 out of the 17 non-compliant programs. The re-inspections focussed on, but were not restricted to, those sections of the CTO Regulations where deficiencies were observed during the regular inspection.

As of June 2012, 98% of all registered CTO programs inspected were overall compliant with the CTO Regulations. The remaining 2%, which represents two CTO programs, that received an overall non-compliant rating during their regular inspection, will be re-inspected to re-assess their compliance with the CTO Regulations prior to issuing a new rating. The corrective actions submitted by these two non-compliant programs, however, have been assessed and found to be acceptable.

During the 140 inspections (125 regular and 15 re-inspections) conducted in the period covered in this report, a total of 2404 observations were noted. The majority of observations (81.2%) were cited against requirements for donor suitability assessment (Section 18 – 23), packaging and labelling (Section 28 – 33) and quality assurance system (Section 70 – 76).

The second round of inspections began in April 2012. During this round, Health Canada began classifying individual observations as critical, major, or minor. This is in addition to the overall rating of compliant or non-compliant that is assigned following an inspection. The intent is to provide additional information to establishments with regard to their level of compliance with the CTO Regulations. All ratings will be 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) (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/cell/gui-0101_doc-eng.php).

Furthermore, to develop an effective and uniform national inspection strategy, Health Canada conducted a consultation that provided stakeholders with the opportunity to comment and provide feedback on different inspection strategy options. A summary of the comments received from stakeholders has been compiled and will be posted on the Health Canada's website along with the final CTO inspection strategy (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/cell/pol-0057_doc-eng.php)in November 2012.

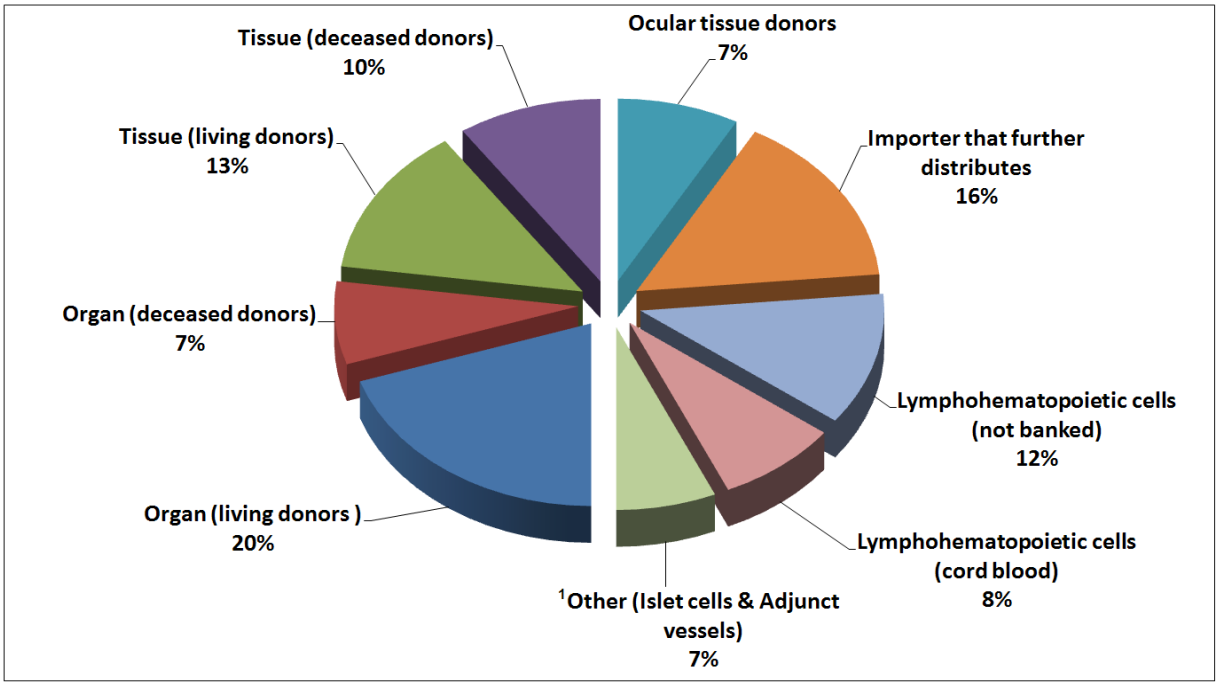
1.0 Background

Health Canada's Health Products and Food Branch Inspectorate (Inspectorate) in partnership with Regions and Programs Bureau (RAPB) is responsible for delivering national compliance and enforcement activities for regulated products under its mandate. The authority to deliver this compliance and enforcement program for these products is derived from the *Food and Drugs Act (Act)* and its *Regulations*, which includes the *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* (CTO Regulations). The Inspectorate's *Compliance and Enforcement Policy* (POL-0001) provides the guiding principles for the application of compliance and enforcement activities under the *Act* and its *Regulations*. It is within this context that registered Canadian human CTO establishments are inspected to assess their compliance with the CTO Regulations.

The CTO Regulations came into force on December 7, 2007, except for subsection 26 (1), which came into force on June 7, 2008. The purpose of the CTO Regulations is to minimize the potential health risks to Canadian recipients of human CTO 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 June 2012, a total of 104 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 are based on 134 registered Canadian CTO programs. Figure 1, below, shows the distribution of the 10 types of Canadian CTO programs that have registered with Health Canada.

Figure 1.0 National distribution of the 10 types of registered Canadian cells, tissues and organ programs



[1]Islet cell programs (2%) and adjunct vessel programs (5%) were combined into "Other" (7%).

Prior to the start of the inspection program, Health Canada held formal information sessions across Canada to increase stakeholder's awareness of the CTO regulatory requirements. In August 2009, Health Canada began inspecting registered Canadian CTO programs to facilitate compliance promotion and to assess their compliance 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. Depending on the severity of the observations, an overall rating of Compliant ("C") or Non-Compliant ("NC") is issued and corrective measures are required for each observation. An "NC" rating has serious consequences for a program, ranging from the implementation of immediate corrective measures to the cancellation of the CTO registration number.

2.0 Definitions and Acronyms

Compliance: The state of conformity of a regulated person (including a corporation, individual or other legal entity) or product with a legislative requirement or a recognized standard.

Compliant ("C"): At the time of the inspection, the regulated party has demonstrated that the activities it conducts are in compliance with the Act and its associated Regulations.

CSA: Canadian Standards Association.

Enforcement: Actions that may be taken to induce encourage or compel compliance with the *FDA* and its associated Regulations.

***Food and Drugs Act* (Act):** A federal statute regulating the health and safety of food, drugs, cosmetics, and medical devices. The Minister of Health is responsible for the administration of the *Act.*

Importer: an establishment that brings in or facilitates the transfer of CTO from a foreign source located geographically outside Canada and further distributes it to CTO establishments in Canada. Health Canada does not consider an establishment to import if the CTO is from inside Canada (for example, from a different province or territory).

Inspection: Compliance monitoring activity undertaken on-site on a predetermined cycle or as required, for the purpose of determining whether or not a regulated party is in compliance with the applicable law.

Inspector: A person designated under section 22 of the *Food and Drugs Act*.

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 Act and its associated Regulations.

Observation: A deviation from or deficiency in compliance with the Act or the CTO Regulations found during the inspection of a CTO establishment. An observation is classified in accordance with the level of risk associated with the deficiency. All observations must be documented in the inspection report (Exit Notice).

Re-inspection: a follow-up inspection carried out in response to the assignment of an NC rating. The inspection is focused on, but not restricted to those regulatory requirements where observations were made.

Registration: An act whereby a person or an establishment gives a formal written record for reference.

Source Establishment: "source establishment" means

a. subject to paragraph (b), in the case of an organ from a deceased donor, the relevant organ donation organization;

b. in the case of adjunct vessels that are retrieved with an organ and not used immediately in the organ transplantation, the relevant tissue bank;
c. in the case of an organ from a living donor or lymphohematopoietic cells that are not banked, the relevant transplant establishment;
d. in the case of tissues or banked lymphohematopoietic cells, the relevant cell or tissue bank; and
e. in the case of islet cells, the establishment that prepares the cells for use in transplantation.

Note: More definitions are available in Section 1 of the CTO Regulations.

3.0 Inspections

The main objective of an inspection is to assess compliance with the CTO Regulations, which set out safety requirements relating to the processing and distribution of human CTO for transplantation. Prior to an inspection, Health Canada provides a pre-inspection package to CTO programs to help them prepare for the inspection and to increase their awareness of the CTO regulatory requirements. In most cases inspections are announced; however, unannounced inspections may be conducted 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. The duration of an inspection varies depending on the type of activities, number of inspectors and size of the program.

In August 2009, Health Canada began inspecting registered Canadian CTO programs with the goal of completing the inspections within 36 months. Table 1 indicates the regional distribution of inspections conducted across Canada. As of June 2012, a total of 125 out of 134 registered Canadian CTO programs have been inspected. Of the 9 registered CTO programs yet to be inspected, 5 are currently not active and may not be inspected until they become active. The remaining 4 active CTO programs will be inspected by March 2013, and the results reported in the next summary report.

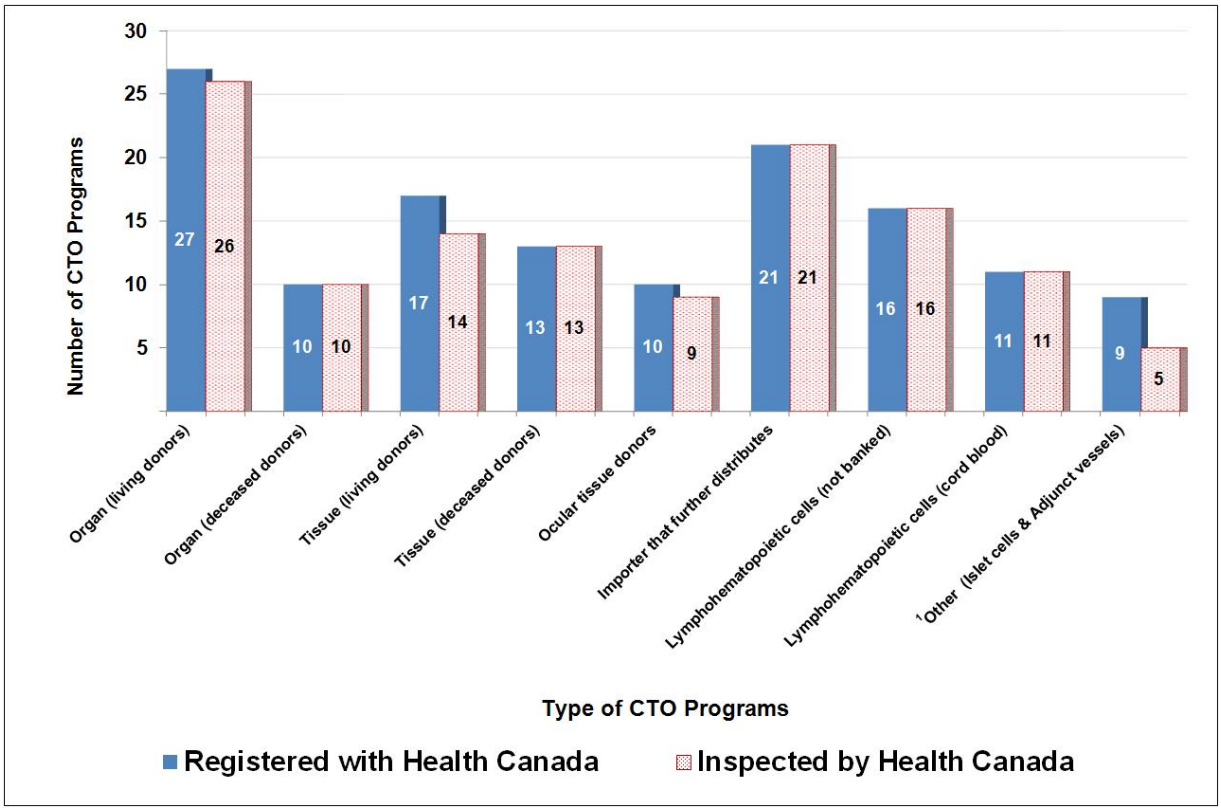
Table 1.0 National distribution of cells, tissues and organ programs registered and inspected by Region (August 2009 – June 2012)

Regional Inspectorate Programs	Registered programs per region (#)	Programs inspected per region (#)
Atlantic Region[1]	11	10
Quebec Region	24	23
Ontario Region[2]	54	47
Manitoba & Saskatchewan Region	13	13
Alberta Region[3]	16	16
British Columbia Region[4]	16	16
Total	**134**	**125**

[1]Atlantic Region = Nova Scotia, New Brunswick, Newfoundland and Labrador and Prince Edward Island; [2]Ontario Region = Ontario and Nunavut Territory; [3]Alberta Region = Alberta and Northwest Territories; [4]British Columbia Region = British Columbia and Yukon Territory

The status of inspections, based on the 10 types of CTO programs inspected, is depicted by the bar graph below (Figure 2).

Figure 2.0 Inspection status of registered Canadian cells, tissues and organ programs (August 2009 – June 2012)



[1]One Islet cells program and three Adjunct vessels programs were not inspected.

Of the 125 programs inspected, 108 (86%) programs were assigned an overall “C” rating, and 17 (14%) programs were initially found to be overall “NC”. Health Canada worked closely with the programs rated “NC” to bring them into compliance. Where necessary, Health Canada distributed information documents and compliance promotion materials to clarify Health Canada’s expectations with respect to the safety requirements stipulated in the CTO Regulations, and to increase stakeholder awareness. During the period covered in this report, Health Canada re-inspected 15 out of 17 “NC” rated programs. The re-inspections focussed on, but were not restricted to, those sections of the CTO Regulations where violations were observed during the regular inspection. The results of all re-inspections indicated that the implicated programs successfully implemented appropriate corrective measures and hence were found to be in compliance with the CTO Regulations.

As of June 2012, 98% of all registered CTO programs inspected were found to be overall compliant with the CTO Regulations. The remaining 2%, which represents two CTO programs, that received an overall “NC” rating during their regular inspection, will be re-inspected to re-assess their compliance with the CTO Regulations prior to issuing a new rating. Their corrective actions, however, have been assessed and found to be acceptable.

4.0 Analysis of Observations

During the 140 inspections (125 regular and 15 re-inspections) conducted in the period covered in this report, a total of 2404 observations were cited. Table 2 illustrates the grouping of these observations in accordance with the CTO

regulatory requirements. The majority of observations (81.2%) were cited against requirements for donor suitability assessment (Section 18 – 23), packaging and labelling (Section 28 – 33) and quality assurance system (Section 70 – 76).

Table 2.0 Distribution of observations by cells, tissues and organ regulatory requirements (August 2009 – June 2012)

CTO Regulatory Requirements		Distribution of Observations	
		#	%
S.18-23	Donor Suitability Assessment	1126	46.8%
S.28-33	Packaging & Labelling	514	21.4%
S.70-76	Quality Assurance System	312	13.0%
S.55-63	Records	148	6.1%
S.64-69	Personnel, Facilities, Equipment and Supplies	141	5.8%
S. 40-42	Exceptional Distribution	47	2.0%
S.25-27	Testing	45	1.9%
S.15	Source Establishment	20	0.8%
S.43-54	Errors, Accidents and Adverse Reaction Investigation and Reporting	20	0.8%
S.34	Quarantine	9	0.4%
S.5-14	Registration	9	0.4%
S.35-39	Storage	7	0.3%
S.4	Prohibition	2	0.1%
S.24	Retrieval interval - tissues	2	0.1%
S.16	Documented evidence	2	0.1%
Total		**2404**	**100.0%**

4.1 Examples of Observations

Processing: Donor Suitability Assessment (Section 18 to 23)

The donor suitability assessment refers to an evaluation based on donor screening and all donor testing results. It is critical that donors are screened to elicit general health information and to identify risks that could impact the safety of CTOs. Deficiencies relating to incomplete donor suitability assessment accounted for 46.8% of all observations cited.

Examples of observations cited against donor suitability assessment include:

Example 1: The establishment did not perform all the required steps in assessing the suitability of living organ donors, for example:

a) There was no documented evidence to indicate that the donor information and history was obtained in accordance with section 12.2.2.3 of the organ standard.

b) The establishment did not perform hepatitis B virus (HBV) testing on a donor blood specimen collected within one month prior to donation for (organ) donor ID ####. It is acknowledged that HBV testing was previously performed. However, the collection date is stated as “unknown” on the test results report.

c) Prior to yy-mm-dd, the laboratory was not repeating any initial reactive results for the Hepatitis B Surface Antigen test (HBsAg). Instead, the laboratory would proceed to the HBsAg confirmatory test and if the result of the confirmatory test was negative, then this negative result would be the only result reported for the HBsAg test.

d) The donor assessment questionnaire did not include all exclusionary criteria regarding high risk behaviour as stated in Annex E of CAN/CSA-Z900.1, as follows:
   - Persons who have had sex in the preceding 12 months with a person known or suspected to have human immunodeficiency virus (HIV) , clinically active HBV or hepatitis C virus (HCV)
   - Persons who have been exposed in the preceding 12 months to known or suspected HIV-, HBV- and/or HCV- infected blood through percutaneous injection or through contact with an open wound, non-intact skin or mucous membrane

Example 2: Testing requirements, as set out in 12.2.2.4 of the Lymphohematopoietic Standards, were not always met. For example, the date and time of collection of maternal blood specimens was not recorded in any of the six files reviewed. Therefore, it could not be ascertained if maternal blood specimens were taken at the time of, or within seven days following, collection of the cord blood unit.

Packaging and Labelling (Section 28 to 33)

Packaging must ensure integrity of the CTOs and labelling must maintain traceability of CTOs throughout the chain of distribution. Establishments must include specific information on the exterior/interior labels and package inserts to facilitate flow of information among all establishments involved in the chain of distribution. Some of the required information from the source establishment to any other establishment include: donor identification code; source establishment's information such as name and address and contact information; processing information relevant for transplantation (for example, donor's ABO group, anticoagulant, storage solution); a statement that the CTO has been declared safe for transplantation; and, where applicable, expiry date and time and storage conditions for CTOs. Deficiencies relating to inadequate packaging or labelling accounted for 21.4% of all observations cited.

Examples of observations cited against these sections include:

Example 1: The package insert that accompanied the tissue from the tissue bank to the transplant establishment was incomplete in that it did not include all required information, as follows:
- The donor identification code, clearly labelled as such.
- A statement that the tissue has been irradiated. The bone bank's documentation states that a secondary sterilization was performed by gamma radiation; however this does not occur for tendons.
- Statement that the tissue has been declared safe for transplantation.
- Instructions on how to report errors/accidents.
- The source establishment's civic address and contact information.

Example 2: The exterior label that accompanied the tissue from the tissue bank to any other establishment did not contain the following information: the registration number of the source establishment, the statement "human tissue for transplant" and handling instructions for storage and for storage during transportation.

Quality Assurance System (Section 70 to 76)

A Quality Assurance System (QAS) defines the policies and procedures that provide confidence that the CTOs processed and distributed consistently conform to the safety requirements outlined in the CTO Regulations. Elements of QAS include, but are not limited to, quality control, auditing and process control, standards for personnel, facilities, procedures, equipment and testing. A QAS is required to ensure that all activities are conducted and documented as per regulatory requirements. Deficiencies relating to QAS accounted for 13% of all observations cited.

Examples of observations cited against these sections include:

Example 1: The establishment has not audited all regulated activities every two years to verify that these activities comply with the CTO Regulations and with the establishment's standard operating procedures.

Example 2: Although testing was performed, the procedure was incomplete as the list of required serology tests did not include tests for antibodies to hepatitis C virus and total antibody to hepatitis B core antigen.

Example 3: The procedure for documentation and reporting of errors or accidents did not include notification of the source establishment for imported tissue as per section 43 of the regulations. In addition, the procedure did not include instructions on actions to be taken upon receiving notification of an error or accident as per section 46.

Example 4: Some of the standard operating procedures did not reflect the regulatory requirements of the CTO Regulations. For example:

a) The donor suitability assessment procedure did not require that the results of infectious disease testing be reviewed prior to determining the suitability of a donor to donate.

b) The exceptional release criteria SOP did not require that the following information be recorded on the notice of exceptional distribution:
   - The justification for the distribution that formed the basis for the transplant physician's decisions to authorize it;
   - The time of the written authorization of the distribution and the time of distribution.

c) The processing of maternal blood samples procedure did not specify the time frames for the collection of maternal blood specimens.

Example 5: The relevant standard operating procedures were not available at all locations where activities were performed.

5.0 Conclusion

During the period covered in this report, Health Canada inspected 125 registered Canadian CTO programs. Overall, 98% of these programs were assigned an overall compliant rating. The remaining 2%, which represents two non-compliant programs, have submitted corrective actions and were found to be acceptable. Health Canada will re-inspect both implicated CTO programs to re-assess their compliance with the CTO Regulations prior to issuing a compliance rating.

During these inspections, the majority of observations (81.2%) were cited against requirements for donor suitability assessment (Section 18 – 23), packaging and labelling (Section 28 – 33) and quality assurance system (Section 70 – 76). By providing examples of these deficiencies cited during inspections, Health Canada aims to promote regulatory compliance, maintain transparency, and increase stakeholder's awareness of common deficiencies.

Inspections are a key component in the delivery of compliance and enforcement activities. The second round of inspections began in April 2012. For this round of inspections, Health Canada has two goals: promote uniformity in the assignment of overall rating, and implement an inspection strategy that will align the level of oversight with the level of risk.

To promote uniformity in the assignment of overall ratings, Health Canada has developed a guidance document to explain the risk classification of an observation assigned to a CTO program during an inspection. *Guidance on Classification of*

Observations for Inspection of Cells, Tissues, and Organs Establishments (GUI-0101) [http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php] was adopted in April 2012, and is posted on Health Canada's website. This document will ensure that each observation cited is associated with a risk level. This will ensure that the overall compliant or non-compliant rating of the establishment is based on the cumulative risk rating for each observation noted.

To ensure that the level of oversight is proportionate to the level of risk, Health Canada has developed an inspection strategy. During the development of this inspection strategy, Health Canada held a stakeholder consultation which provided stakeholders with the opportunity to comment and provide feedback on different inspection strategy options presented to them. A summary of the comments received from stakeholders has been compiled and will be posted on the Health Canada's website along with the final inspection strategy in November 2012 (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/cell/pol-0057_doc-eng.php).

6.0 References

1. *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* (CTO Regulations) (http://laws-lois.justice.gc.ca/eng/regulations/SOR-2007-118/)

2. *Guidance Document for Cells, Tissues and Organs Establishments - Safety of Human Cells, Tissues and Organs for Transplantation* (GUI-0082). (http://hc-sc.gc.ca/dhp-mps/brgtherap/reg-init/cell/cto_gd_ld-eng.php)

3. *Compliance and Enforcement Policy* (POL-0001), Health Products and Food Branch Inspectorate. (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/pol/pol_1_tc-tm-eng.php)

4. *Guidance on Classification of Observations for Inspection of Cells, Tissues and Organs Establishments* (GUI-0101) (http://hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/cell/gui-0101_doc-eng.php)

5. *Food and Drugs Act* (FDA) (http://laws-lois.justice.gc.ca/eng/acts/F-27/)