Health Canada Santé Canada

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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

Guidance on Classification of Observations for Inspection of Cells, Tissues and Organs Establishments

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1.0 Purpose

This document is an administrative tool and is intended to:

- Assist in the classification of observations made during inspection of Cells, Tissues and Organs (CTO) establishments.
- Promote uniformity in the assignment of ratings to individual observations, and to overall inspection ratings of the CTO establishments.
- Provide examples of situations of non-compliance with the *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* (CTO Regulations).

This document should be read in combination with the *Food and Drugs Act* (Act), CTO Regulations, the referenced sections of the General Standard CAN/CSA Z900.1 entitled, *Cells, Tissues, and Organs for Transplantation and Assisted Reproduction: General Requirements*, along with the subset of National Standards for lymphohematopoietic cells, perfusable organs, tissue and ocular tissues and the *Guidance Document for Cells, Tissues and Organs Establishments - Safety of Human Cell, Tissue and Organ for Transplantation*.

2.0 Background

The CTO Regulations were made pursuant to the Act. The CTO Regulations directly reference sections of the National Standard thus making them mandatory. The purpose of this regulatory initiative is to minimize the potential health risks to Canadian recipients of human cells, tissues and organs. The CTO Regulations address safety in the processing and handling of these products, resulting in improved protection of the health and safety of Canadian transplant recipients. The CTO Regulations were published on June 27, 2007 and came into force on December 7, 2007, except for subsection 26(1) which came into force on June 7, 2008.

Health Canada conducts inspections of CTO establishments under the authority of Section 23 of the Act. Inspections are an important part of a national compliance and enforcement program.

During the first round of inspections, Health Canada inspected Canadian registered CTO programs to assess their compliance with the CTO Regulations and assigned an overall rating to each establishment.

Effective April 2012 individual observations will also be assigned a classification (e.g. critical, major or minor). This is in addition to the overall rating (e.g. Compliant or Non-Compliant) that will be assigned following an inspection. The intention is to provide more information to establishments with regards to their level of compliance with the CTO Regulations. All ratings will be assigned in accordance with the principles and guidelines set forth in this document.

3.0 Scope

This guidance document applies to inspections of all CTO establishments regulated under the CTO Regulations. The attached appendix provides examples of situations or observations and their assigned risk classification. Classification of an observation is determined by the inspector using his or her judgment in consultation with this document and other relevant documents and information. Please note that the list in the appendix is not exhaustive and additional situations or observations may be added where appropriate.

4.0 Definitions and Acronyms

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

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**).

The observations are classified as Critical, Major or Minor.

Critical observation (Risk 1):

- Any observation that directly affects the safety of the product(s) and is likely to result in an immediate or latent health risk to the recipient; or

- Fraud, misrepresentation or falsification of product(s) or data.

Major observation (Risk 2):

- Any observation that potentially affects the safety of the product(s) and could result in an immediate or latent health risk to the recipient.

Minor observation (Risk 3):

- Any observation that has low or negligible impact on the safety of the product(s).

All observations cited in the Exit Notice will be assigned a numerical rating based on their classification: Risk 1 for Critical observations, Risk 2 for Major observations and Risk 3 for Minor observations.

C (Compliant): 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.

Disclaimer - *A Compliant rating does not mean that there are no observations or corrective actions required.*

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

5.0 Guide

5.1 Assigning a Risk Classification to an Observation

Observations are classified as Critical, Major or Minor. The classification will be assigned based on the impact on the safety of the CTO. The following are examples of criteria that are taken into consideration:

- potential or immediate health risk;
- nature of the non-compliance;
- number of occurrences of a particular non-compliant issue; and
- context of the situation.

The Appendix lists examples of situations that will lead to an observation. Although the specific examples given in the Appendix are assigned a particular rating, the same situation could be assigned a higher or lower rating depending on the nature and extent of the deficiency. The examples are intended to illustrate the process by which an inspector assigns a rating to his or her observations and are not intended to limit the discretion of an inspector in determining compliance with the Act and CTO Regulations. For example, observations that are repeated from previous inspection(s) may be assigned a different classification than referenced in the Appendix.

5.2 Determining the Establishment's Overall Compliance Rating

The inspector will assign an overall rating of compliant or non-compliant as defined in section 4.0 of this document.

Generally the following criteria may apply when assessing the overall compliance rating;

Compliant (C):

- No observations are made.
- Only Minor observations are made.
- A few Major observations are made and immediate corrective actions have been implemented when required.

Non-Compliant (NC):

- One or more Critical observations are made.
- Several Major observations are made which indicate that the establishment does not adequately control its regulated activities.
- Failure to implement corrective measures for Critical or Major observations made in previous inspection.

When a Critical observation is noted during an inspection, Health Canada will bring this serious situation to the attention of the establishment's Medical Director and/or qualified staff. The establishment will be duly informed that this may result in an "NC" rating. An action plan specifying corrective measures to be taken as well as the time frame necessary to implement these actions will be requested. An NC rating will have serious consequences for an establishment and may result in the cancellation of the registration of the CTO establishment. Enforcement actions will be taken as required and in accordance with Health Canada's *Compliance and Enforcement Policy*, POL-0001.

6.0 References:

Safety of Human Cells, Tissues and Organs for Transplantation Regulations (CTO Regulations).

Guidance Document for Cells, Tissues and Organs Establishments - Safety of Human Cells, Tissues and Organs for Transplantation.

National Standard of Canada CAN/CSA-Z900.1 entitled *Cells, Tissues, and Organs for Transplantation and Assisted Reproduction: General Requirements.*

National Standard of Canada CAN/CSA-Z900.2.2 entitled, *Tissues for Transplantation*.

National Standard of Canada CAN/CSA-Z900.2.3 entitled, *Perfusable Organs for Transplantation.*

National Standard of Canada CAN/CSA-Z900.2.4 entitled, *Ocular Tissues for Transplantation.*

National Standard of Canada CAN/CSA-Z900.2.5 entitled, *Lymphohematopoietic Cells for Transplantation.*

Appendix

Potential Observations and Assigned Ratings

Prohibition (Section 4)

Critical:

- An establishment transplanted a CTO that was not determined safe for transplantation.
- An establishment transplanted tissues that were not processed by a registered establishment.
- An establishment imported tissues that were not processed by a registered establishment.

Registration (Sections 5 to 14)

Major:

- The establishment did not register all the types of CTO that they were processing.

Minor:

- The establishment did not notify the Minister in writing within the required timeframe, of the changes in the information provided in the registration.

Source Establishment (Section 15)

Major:

- There was no documented evidence to indicate that the source establishment reviewed the processing activities performed by other entities on their behalf for completeness and compliance with the CTO Regulations.
- There was no documented evidence that the donor suitability assessment was reviewed by the source establishment to determine that the CTO were safe for transplantation.

Processing – General (Sections 16-17)

Major:

- No documented evidence to demonstrate validation of activities, processes or technical procedures where necessary.
- Although the validation study was completed, not all parameters or products were included.

Minor:

- Although the validation data was performed by qualified staff, there was no evidence that a final review was completed.

Processing - Donor Suitability Assessment (Sections 18 to 23)

Critical:

- There was no evidence that a physical exam was performed.
- There was no evidence to indicate that a required infectious disease marker test was performed, yet the CTO from the donor were distributed.
- There was no evidence that the donors were assessed against all exclusion criteria.
- There was no evidence that the minimal serological testing was conducted within the required timeframe.

Major:

- The physical examination did not address all the requirements of section 13.2 of the CSA General Standard CAN/CSA-Z900.1.
- The Donor Medical Social History Questionnaire included all the questions required by the exclusion criteria; however a response was not recorded for some of the questions.

Processing - Retrieval (Section 24)

Major:

- The retrieval time exceeded the established maximum interval between the cardiac asystole of the donor and the retrieval of the tissue.

Processing - Testing (Sections 25 to 27)

Critical:

- The test kit that was used for donor testing was not licensed.

Major:

- The test kit that was used for testing tissue donors was licensed as a diagnostic test kit rather than for donor screening as required.

Processing - Packaging and Labelling (Sections 28 to 33)

Critical:

- The tissue bank did not include the donor identification code on the package insert and on the interior label as required.

Major:

- The donor identification code was present on the interior label but not on the package insert when it was distributed from the tissue bank to other establishments.

Minor:

- The contact information of the transplant Establishment was not identified on the exterior label, as required; however, the retrieval establishment, the source establishment and the transplant establishment are located within the same hospital.

- There was no process in place to verify if the packaging material is free of damage.

- Although exceptional distribution was used, the package insert did not include the statement "For Exceptional Distribution", the reason for exceptional distribution or how the cells did not meet the requirements of the CTO Regulations, as required. All other provisions of the exceptional distribution requirements were met.

Processing - Quarantine (Section 34)

Major:

- Although the donor suitability assessment was completed, there was no evidence to indicate that the processing records were reviewed for completeness and compliance with the Regulations and the standard operating procedures prior to the release of tissues from quarantine.

- Tissues from a living donor were not quarantined for at least 180 days when the initial testing did not include nucleic acid testing (NAT) for HIV-1 and HCV.

- The stored cord blood unit was not designated as quarantined although it had not been determined safe for transplantation under the CTO Regulations.

Minor:

- The final report verifying bacteriological test result was not found in the donor file; however another copy of that report was obtained from the lab during the inspection.

- Although qualified staff verified and accepted each of the donor suitability criterion, there was no process and/or control in place to ensure that the final donor suitability assessment was performed.

Storage (Sections 35 - 39)

Critical:

- The establishment did not take action following a significant deviation of temperature range in the released tissue freezer.

Major:

- Records indicate that the temperature of the quarantine and release storage equipment was not consistently monitored to ensure the acceptable temperature range was maintained.

- Autologous tissues were stored with released allogeneic tissues without the autologous tissues being clearly labelled “For autologous use only”.

- CTO were stored in a room that was not being monitored to ensure that the appropriate environmental conditions were being maintained as per the requirements specific to the CTO.

- There were no records to indicate that the time period used to store adjunct vessels, which were not used immediately in the organ transplantation, had been determined based on scientific evidence.

- The tissue storage area was not secured to prevent the entry of unauthorized persons.

Minor:

- The quarantine and release freezers were monitored daily; however the documentation of the preventative maintenance program was not available for review.

Exceptional Distribution (Sections 40 - 42)

Critical:

- There was no evidence to indicate that the source establishment distributed the tissue under the exceptional distribution provisions where required by the CTO regulations.

Minor:

- The notice of Exceptional Distribution did not include the name of the transplant establishment.

Error, Accident and Adverse Reaction Investigation and Reporting (Sections 43 - 54)

Critical:

- An error and accident investigation related to an unexpected adverse reaction involving a transmission of an infectious disease was not initiated by the source establishment.

- Tissues were released from quarantine prior to the completion of the error and accident investigation.

Major:

- Although errors and accidents related to transmissible disease testing were investigated, the detailed final report was not submitted to the Minister by the source establishment.

Records (Section 55 - 63)

Critical:

- There was no record that donor suitability assessment was completed.
- There was no record identifying to which establishment the adjunct vessels were distributed.

Major:

- The tissue retrieval form was completed by an employee not directly involved in the retrieval procedure.

Minor:

- The donor suitability documentation received by fax was not legible. The information was verified verbally but not documented.
- Shipping records of the distributed tissues were not consistently retained by the establishment.

Personnel, Facilities, Equipment and Supplies (Section 64 - 69)

Major:

- There was no documentation for the installation qualification of the newly acquired automated system used to process cord blood.
- There were no training records or competency evaluations for staff performing the regulated activities in the establishment.
- The insulated box containing the collection kit for cord blood has not been adequately qualified for the maintenance of appropriate environmental conditions.
- The room where aseptic processing activities were being performed was not subject to microbiological monitoring and control.
- The expiry date of critical supplies was not strictly observed.
- The refrigerator used to store the tissues for transplantation was not being monitored to ensure that appropriate environmental conditions were maintained.

Minor:

- The training records were incomplete.

Quality Assurance System (Sections 70 - 76)

Critical:

- There was no Quality Assurance System in place.

Major:

- There was no policy or procedure to describe when testing of both the infant donor and the mother is required.

- The establishment did not have a procedure in place for conducting the donor suitability assessment.

- The deceased donor screening policy did not provide guidance on how to assess responses to questions in the medical, social and behavioural history questionnaire that were marked as "unknown".

- There was no procedure in place for investigating, quarantining of CTO (if required) and reporting suspected error and accident to other implicated establishments as required.

- The establishment had not conducted an audit to verify that all activities carried out comply with the CTO Regulations and with its standard operating procedures, by a person who does not have direct responsibility for the activities being audited.

- There was no evidence to indicate that the establishment reviewed the standard operating procedures impacting the safety of the CTO every two years.

- There was no policy or procedure in place to apply exceptional distribution provisions as required by the CTO Regulations.

Minor:

- Although it was documented that the designated hospital staff are trained and knowledgeable on labelling requirements, a copy of the current labelling procedure was not available at the locations where the activities were performed.

- The "Record" section of the standard operating procedures did not indicate to keep the records for the required 10 years.