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Guidance Document

Safety of Human Cells, Tissues and Organs for Transplantation Regulations

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Health Canada is the federal department responsible for helping the people of Canada maintain and improve their health. Health Canada is committed to improving the lives of all of Canada's people and to making this country's population among the healthiest in the world as measured by longevity, lifestyle and effective use of the public health care system.

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Foreword

Guidance documents provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. They also provide guidance to Health Canada staff on how mandates and objectives should be met fairly, consistently and effectively.

Guidance documents are administrative, not legal, instruments. This means that flexibility can be applied. However, to be acceptable, alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate justification. They should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As always, Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, to help us adequately assess the safety, efficacy or quality of a therapeutic product. We are committed to ensuring that such requests are justifiable and that decisions are clearly documented.

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1. Overview

1.1 Purpose

The *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* (CTO regulations) contain safety requirements for:

- processing
- storage
- keeping records
- distribution
- importation
- investigating and reporting errors, accidents and adverse reactions

Processing includes the following activities:

- donor screening
- donor testing
- donor suitability assessment
- retrieval, except for organs and islet cells
- testing and performing measurements on cells, tissues or organs after they are retrieved
- preparing cells and tissues for use in transplantation
 - does not apply to organs
- preserving, quarantining and banking
- packaging and labelling

The CTO regulations are intended to improve protections for the health and safety of people in Canada who receive transplants.

Health Canada's Biologic and Radiopharmaceutical Drugs Directorate, Health Products and Food Branch, administers the CTO regulations. If you have questions about the regulations or this guidance document, please email us: brdd-cppic_brdd-cppci@hc-sc.gc.ca.

1.2 Scope and application

The CTO regulations apply only to human cells, tissues and organs that are to be used in transplantation. Cells, tissues and organs donated for different purposes, such as for education or non-clinical research, are not within the scope of these regulations.

This guidance document outlines the scope of the CTO regulations as well as the activities they govern. It is an important point of reference to help readers determine whether a product and the activities related to it are governed by the CTO regulations. It also gives details on what the current safety requirements for cells, tissues and organs used in transplantation must be fulfilled.

This guidance document supersedes previous documents.

The CTO regulations apply to individuals and establishments that handle, process, distribute or import human organs, or minimally manipulated cells and tissues for homologous (same basic

function after transplantation) use, for transplantation in a person. To fully comprehend these regulations, you must also consult the:

- *Food and Drugs Act*
- national standard on cells, tissues and organs for transplantation, published by the Canadian Standards Association

It is your responsibility to make sure you are accessing the most recent version of:

- the CTO regulations
- the national standard
 - which is incorporated by reference into the regulations
- this guidance document

1.3 Policy objectives

The purpose of this regulatory framework is to minimize the potential health risks to people in Canada who receive human cells, tissues and organs. This guidance document interprets the CTO regulations.

1.4 Background

These regulations establish safety requirements for processing and handling human cells, tissues and organs for transplantation. These requirements will improve protections for the health and safety of people in Canada who receive transplants.

The CTO regulations are based on the national standard as well as information obtained during extensive consultations with the provinces, territories and transplantation experts. We used a risk management approach to develop the regulations. Through international regulatory cooperation, the national standard is available for other nations to model.

The following are mandatory as they are referenced directly in the CTO regulations:

- sections of the general standard CAN/CSA Z900.1, "Cells, Tissues, and Organs for Transplantation: General Requirements"
- sections of the subset standards for specific organ and tissue types
 - lymphohematopoietic cells, perfusable organs, tissues and ocular tissues

Note: The national standard speaks to various aspects of the donation and transplantation process. However, our scope for cells, tissues and organs is limited to activities related to product safety and quality assurance. Every section of the national standard that is referenced in the CTO regulations concerns the safety or quality of cells, tissues and organs. The regulations do not reference sections of the national standard that concern the practice of medicine, which does not fall under federal jurisdiction.

The CTO regulations set out safety requirements for:

- processing, which includes:
 - screening and testing donors
 - collecting and retrieving cells, tissues and organs
 - preserving, packaging, labelling and quarantining
- storing
- keeping records
- distributing
- importing
- investigating and reporting on errors, accidents and adverse reactions

The regulations are designed to maximize the safety of cells, tissues and organs. They clearly outline the safety requirements adopted from the national standard, thus making them mandatory. Referencing the national standard provides a consistent and safety-focused regulatory framework that will minimize the risks to people in Canada who receive cells, tissues and organs.

CSA Group national standard

You can order the Z900 package of the national standard by calling 1-800-463-6727 or visiting the [CSA Group website](#). The CTO regulations are standard-based. This means that CTO establishments:

- must comply with sections of the national standard referenced in the regulations
- should have the most updated version of the standard, to access the latest regulatory requirements

The regulations incorporate by reference the applicable standards as amended from time to time. Amendments to the national standard will be sent to establishments that have registered their package with the CSA Group.

Find out more on how to register your national standards and receive updates by consulting the [CSA Group standards update service page](#).

The field of CTO donation and transplantation is changing as the science evolves. Thus, we are basing our regulatory framework on the standards. A committee of transplantation experts and interested stakeholders developed the national standard together. This consensus-driven process may enhance future compliance.

All stakeholders play a key role in keeping the standards up to date. Each subset of the CSA Group national standard contains a Proposal for Change Form. Stakeholders may use this form to submit proposals for change directly to the CSA Group. Along with the appropriate contact information, the CSA Group asks that stakeholders supply the following information, to help them evaluate proposed changes:

- standard/publication number
- relevant clause, table and/or figure number(s)
- wording of the proposed change
- rationale for the change

Acronyms

CMV: cytomegalovirus

CSA: CSA Group

CTOs: cells, tissues and organs

EBV: Epstein-Barr virus

HBV: Hepatitis B virus

HCV: Hepatitis C virus

HIV: Human Immunodeficiency virus

HLA: human leukocyte antigen

HTLV: Human T-Lymphotropic virus

MDALL: Medical Devices Active Licence Listing

NAT: nucleic acid testing

ROEB: Regulatory Operations and Enforcement Branch (formerly Health Products and Food Branch Inspectorate)

WNV: West Nile virus

2. Implementation

"Should" indicates a recommendation made by Health Canada. Where standards are recommended, an establishment should use a risk-benefit analysis on which to base decisions on their implementation.

Note: The *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* (CTO regulations) specify minimum safety standards, which CTO establishments may exceed. The statements, definitions and tables on labelling requirements under sections 30 to 32 are taken directly from the CTO regulations.

1.1 Interpretation

Section 1

This section lists the terms used in the CTO regulations.

Accident:

An unexpected event that:

- is not attributable to a deviation from the standard operating procedures or applicable laws and

- could adversely affect the safety of a transplant recipient or the safety, efficacy or quality of cells, tissues or organs

Act:

Refers to the *Food and Drugs Act*.

Adverse reaction:

An undesirable response in the recipient to transplanted cells, tissues or organs, including the transmission of a disease or disease agent.

Banked:

For cells and tissues, means processed cells and tissues that:

- have been determined safe for transplantation and
- are stored by the source establishment in its inventory and available for distribution or transplantation

Cell:

The fundamental biological unit of a human organism that's for use in transplantation.

Distribute:

Does not include to transplant.

Donor:

A living or deceased person from whom cells, tissues or organs are retrieved.

Donor assessment record:

Includes the donor screening, any available donor testing results, information obtained from the donor's medical records and a copy of the donor consent.

Donor identification code:

The unique numeric or alphanumeric designation that:

- is assigned by the source establishment to a donor under section 56 and
- associates each cell, tissue and organ, or part of one, to that donor

Donor screening:

An evaluation based on the donor's medical and social history and physical examination, the results of any diagnostic procedures performed and, if applicable, the autopsy.

Donor suitability assessment:

An evaluation based on the donor screening and

- a. for lymphohematopoietic cells, tissues and organs retrieved from live donors and of tissues retrieved from deceased donors, all donor testing results and
- b. for fresh skin, islet cells and organs retrieved from deceased donors, the donor testing results that are necessary at the time of transplantation

Donor testing:

The laboratory tests and measurements done on a donor or donor specimen to determine all of the following:

- if the donor has or ever had a transmissible disease or is or ever was infected with a transmissible disease agent
- donor compatibility and
- the degree of functionality of the cell, tissue or organ that is to be retrieved

Error:

A deviation from the standard operating procedures or applicable laws that could adversely affect the safety of a transplant recipient or the safety, efficacy or quality of cells, tissues or organs.

Establishment:

A person, a partnership or an unincorporated entity, or a part of any of them, that carries out any of the following activities in respect of cells, tissues or organs:

- importation
- processing
- distribution and
- transplantation

Exceptional distribution:

The distribution under sections 40 to 42 of cells, tissues or organs that have not been processed under these regulations.

Exterior label:

The label that is affixed to the exterior package.

Exterior package:

The outermost package in which a cell, tissue or organ is delivered, transported or shipped.

General standard:

Canada's national standard CAN/CSA-Z900.1, "Cells, Tissues, and Organs for Transplantation: General Requirements", as amended from time to time.

Homologous:

in respect of a cell, tissue or organ, means that the cell, tissue or organ performs the same basic function after transplantation.

Interior label:

The label that is affixed to the interior package.

Interior package:

The innermost package of a cell, tissue or organ that has a non-sterile exterior.

Lymphohematopoietic standard:

Canada's national standard CAN/CSA-Z900.2.5, "Lymphohematopoietic Cells for Transplantation", as amended from time to time.

Medical director:

With respect to an establishment, means a physician or dentist who is:

- licensed under the laws of the jurisdiction in which the establishment is situated to provide health care or dental care and
- responsible for the application of the standard operating procedures and for all medical or dental procedures carried out there, as the case may be

Minimally manipulated:

- in respect of a structural tissue, that the processing does not alter the original characteristics that are relevant to its claimed utility for reconstruction, repair or replacement and
- in respect of cells and nonstructural tissue, that the processing does not alter the biological characteristics that are relevant to their claimed utility

Ocular standard:

Canada's national standard CAN/CSA-Z900.2.4, "Ocular Tissues for Transplantation", as amended from time to time.

Organ:

A perfusable human organ for use in transplantation, whole or in parts, and whose specific function is intended to return after revascularization and reperfusion. Includes adjunct vessels that are retrieved with the organ for use in organ transplantation.

Organ standard:

Canada's national standard CAN/CSAZ900-Z900.2.3, "Perfusable Organs for Transplantation", as amended from time to time.

Package insert:

The document that the source establishment prepares to accompany a cell, tissue or organ.

Note: This may also refer to the package insert the establishment prepares in accordance with the standard operating procedures.

Processing:

For cells, tissues and organs, means any of the following activities:

- donor screening
- donor testing
- donor suitability assessment
- retrieval, except for organs and islet cells

- testing and measurements performed on the cells, tissues or organs after they are retrieved
- preparing for use in transplantation, except for organs
- preservation
- quarantine
- banking
- packaging and labelling

Retrieval:

Under the CTO regulations, a source establishment is responsible for retrieving cells and tissues. For organs, retrieval is not considered processing, and thus is not the responsibility of the source establishment.

Organ retrieval is a surgical procedure that's adapted to the donor organ and the needs of the recipient. It is considered to be within the domain of medical practice.

Health Canada does not regulate medical practice. Thus, the retrieval of organs and islet cells is exempt from the definition of processing. While the retrieval of a pancreas for further processing is exempt from the definition of processing, activities associated with isolating islet cells are captured under the definition of processing since it is considered preparation for use in transplantation.

Post-retrieval testing and measurements performed on the cell, tissue or organ includes, for example, bacteriological testing and biopsy results of the cells, tissues and organs, if performed.

Preparing for use in transplantation:

Source establishments are responsible for preparing cells and tissues for use in transplantation, except final preparation. This is done by the transplant program at the time of transplantation.

Preparing cells and tissues may include:

- cutting or sizing
- dissecting
- centrifugation
- lyophilization
- irradiation

Also included are:

- depleting plasma and red blood cells from lymphohematopoietic cells
- activities that are part of the processing of lymphohematopoietic cells before cryopreservation

Preparing organs for use in transplantation is not considered processing, and is not the responsibility of the source establishment.

As stated in the retrieval section, the preparation that an organ undergoes for use in transplantation is adapted to the donor organ and the needs of the recipient. This is within the domain of medical practice, which Health Canada does not regulate.

Also stated, retrieving a pancreas for further processing is exempt from the definition of processing. However, the activities associated with isolating islet cells are not exempt, as they are considered preparation for use in transplantation. Apart from this distinction, islet cells are regulated according to the same criteria as organs. This means the same donor screening and testing requirements apply to organs and islet cells.

Preservation:

Preservation (for example, cryopreservation, lyophilization) is the act or process of preserving cells and tissues or keeping them from deteriorating or decaying before they're used in transplantation.

Banking:

Banking is storing processed cells and tissues (including adjunct vessels that are not used immediately for transplantation with the organ with which they were distributed). This is done by the source establishment after all other processing activities have been completed in accordance with the regulations.

Cells and tissues that are stored by an importer for further distribution or by an end user establishment for transplantation after the source establishment has released them from their inventory are not considered banked.

Storing lymphohematopoietic cells collected from bone marrow or peripheral blood is not considered banking if the donation is intended to be used to treat a designated recipient.

Note the following definitions that apply to this section.

Quality assurance system:

The coordinated activities of an establishment that relate to the safety of cells, tissues and organs. It includes:

- the standard operating procedures
- records to demonstrate that the standard operating procedures have been implemented and
- audit processes to verify that the standard operating procedures are being implemented

Scientific director:

For an establishment, means an individual who is responsible for the application of the standard operating procedures and for all technical procedures carried out there.

Serious adverse reaction:

An adverse reaction that results in any of the following consequences for the recipient:

- in-patient hospitalization or its prolongation
- persistent or significant disability or incapacity
- medical, dental or surgical intervention to preclude a persistent or significant disability or incapacity
- a life-threatening condition and
- death

Source establishment:

- a. subject to paragraph b), for an organ from a deceased donor, the relevant organ donation organization
- b. for adjunct vessels that are retrieved with an organ and not used immediately in the organ transplantation, the relevant tissue bank
- c. for an organ from a living donor or lymphohematopoietic cells that are not banked, the relevant transplant establishment
- d. for tissues or banked lymphohematopoietic cells, the relevant cell or tissue bank and
- e. for islet cells, the establishment that prepares the cells for transplantation

Standard operating procedures:

The component of the quality assurance system that comprises instructions that set out the processes and procedures to follow in carrying out the activities of an establishment.

Tissue:

A functional group of human cells for use in transplantation. Includes the cells and tissues listed in the definition "tissue" in section 3.1 of the general standard, except for paragraphs (g) and (l).

Tissue standard:

Canada's national standard CAN/CSA-Z900.2.2, "Tissues for Transplantation", as amended from time to time.

Transplant:

To implant cells, tissues or organs into a recipient.

Additional definitions

Importer:

An establishment that brings in or facilitates the transfer of cells, tissues and organs from a foreign source located outside Canada and then distributes to CTO establishments in Canada. An establishment that imports cells, tissues and organs from inside Canada (from a different province or territory) is not an importer. If an establishment only ships cells, tissues and organs for an importer, the shipping company (for example, FedEx) does not have to register as an importer.

Establishment that distributes as an intermediary:

An establishment that further distributes cells, tissues and organs determined safe for transplantation by a source establishment from an establishment to another.

Retrieval establishment:

The organization affiliated with the physical building in which the retrieval takes place. The retrieval team is not necessarily affiliated with the retrieval establishment.

1.2 Application (sections 2 and 3)

Scope of regulations

2. These regulations apply only to organs and minimally manipulated cells and tissues.

Cells and tissues can be manipulated by varying degrees:

- from minimally manipulated cells and tissues
 - such as ocular tissue and fresh frozen tissues
- to more than minimally manipulated cells and tissues
 - such as cells subject to ex-vivo expansion, differentiation and recombinant DNA technology

Cells, tissues and organs for transplantation are generally retrieved from a donor in a functional state. It's expected they will maintain the same function in the recipient, as long as their integrity and function are preserved during processing.

The CTO regulations are based mainly on safety. They do not contain requirements for evaluating clinical effectiveness. For this reason, they only apply to tissues that are minimally manipulated, because such tissues are more likely to maintain their integrity and function during processing.

A minimally manipulated structural tissue (defined in section 1 of the CTO regulations) must still have the characteristics that enable it to carry out reconstruction, repair or replacement.

Examples:

- separating the structural tissue into components whose characteristics relating to reconstruction, repair or replacement are not altered
- extracting or separating cells from structural tissue, where the remaining structural tissue's characteristics relating to achieving reconstruction, repair or replacement are not altered

Other examples:

- lyophilization
- preserving
 - cooling
 - freezing
 - cryopreservation

- chemical preservation
- separating cells
- disinfecting by soaking in antibiotic solution
- cutting/sizing, dissecting, grinding and shaping
- sterilizing by ethylene oxide treatment or gamma irradiation

To be considered minimally manipulated, and therefore included in the scope of the CTO regulations, the structural tissue:

- must not have undergone processing **that alters the original characteristics that are relevant to the claimed utility of the product for reconstruction, repair or replacement**

A tissue characteristic is:

- "original" if it's present in the tissue in the donor
- "relevant" if it could affect how the tissue performs when used for reconstruction, repair or replacement

A minimally manipulated cell or non-structural tissue must still have the biological characteristics (and thus potentially the function or integrity) that are relevant to their claimed utility. Examples of minimal manipulation:

- centrifugation
- cell separation techniques, such as:
 - density gradient separation
 - selective removal of B-cells, T-cells, red blood cells or platelets
- cell selection to enrich the product with CD34+ cells

Other examples:

- freezing
- lyophilization
- cryopreservation

Note: Enzymatic digestion of a pancreas to dissociate islet cells before isolation is minimal manipulation because clinical trials have demonstrated that these cells maintain their biological function. You must notify Health Canada before:

- subjecting islet cells to further manipulation before transplantation
 - for example, by expanding cells or adding drugs, hormones or cytokines
- employing enzymatic digestion for the isolation of other cell types

Our [decision tree](#) will help you determine if a cell or tissue falls under the scope of the CTO regulations.

In some cases, it may be difficult to classify cells and tissues as minimally manipulated or more than minimally manipulated. The decision will have to be made case by case, based on a review of the manufacturing process and/or the availability of clinical data to support their intended use.

For questions on the classification of cells, tissues and organs, please email us: brdd-cppic_brdd-cppci@hc-sc.gc.ca.

To determine which cells, tissues and organs are subject to the regulations, minimally manipulated cells and tissues could be classified further based on other criteria. For example, to be included in the scope of these regulations, minimally manipulated tissues must not meet any of the criteria specified in section 3 of the CTO regulations.

The regulations only apply to minimally manipulated cells and tissues that meet **all** of the following criteria:

- must be intended for allogeneic use, which includes CTOs donated for use by the donor's relatives
- must be intended for homologous use
 - will perform the same function in the recipient as they did in the donor
- must not have a systemic effect and depend on their metabolic activity for their primary function
 - exceptions are noted in subsection 3(1)(d) of the regulations
- must not be combined with non-cell or non-tissue products
 - for example, artificial elements used for tissue engineering
- must have established their safety and effectiveness through historical use or clinical studies

Note: Autologous cells, tissues and organs are not within the scope of the CTO regulations.

Non-application of various therapeutic products:

3. (1) The regulations do not apply to any of the following therapeutic products:

- a. cells, tissues and organs that are for non-homologous use
- b. cells, tissues and organs that are for autologous use
- c. heart valves and dura mater
- d. tissues and cells - except for islet cells and lymphohematopoietic cells that are derived from bone marrow, peripheral blood or cord blood - that have a systemic effect and depend on their metabolic activity for their main function
- e. medical devices containing cells or tissues and are the subject of investigational testing involving human subjects under Part 3 of the *Medical Devices Regulations*
- f. cells, tissues and organs that are the subject of clinical trials under Division 5 of Part C of the *Food and Drug Regulations*
- g. Class IV medical devices that are regulated under the *Medical Devices Regulations*
- h. blood components, blood products and whole blood, except for:

- cord blood and peripheral blood for use in lymphohematopoietic cell transplantation
- i. cells and tissues that are regulated under the *Assisted Human Reproduction Act or any of its Regulations*
- j. semen that is regulated under the *Processing and Distribution of Semen for Assisted Conception Regulations*

Non-application of regulations:

2) No other regulation made under the *Food and Drugs Act* (act) applies to cells, tissues or organs that are the subject of these regulations.

All cells, tissues and organs intended for transplantation are regulated under the act, which provides the authority for developing regulations that are specific for different types of products.

Cells, tissues and organs used for transplantation all share an inherent risk of infectious disease transmission. However, because they vary significantly when it comes to other criteria, they are subject to different regulations developed under the act.

In general, cells and tissues are excluded from the CTO regulations if they meet any of the following criteria:

- are more than minimally manipulated
- are intended for non-homologous use
 - are not intended to perform the same function in the recipient as they did in the donor or
 - there is not enough evidence to prove the intended function is a native characteristic of the cells, tissues and organs
- have a systemic effect and depend on their metabolic activity for their primary function, except for:
 - lymphohematopoietic cells that are derived from bone marrow, peripheral blood or cord blood and islet cells
- are combined with non-tissue products such as artificial elements used for tissue engineering
- are used in investigational studies involving humans, to establish their safety and effectiveness before being used in routine clinical practice
 - for example, some emerging cell or gene therapy products have not been used in the clinical setting for sufficient time and in sufficient quantity to establish their safety and effectiveness for the intended use
- are regulated as drugs or devices under other regulations

Note: Autologous cells and tissues are excluded from the scope of the regulations. However, autologous and allogeneic cells and tissues that meet any of the criteria listed that are for transplantation or assisted reproduction may be subject to federal acts, such as the *Food and Drugs Act* and the *Assisted Human Reproduction Act* and their regulations.

More than minimal manipulation of cells and tissues may involve adding a wide variety of substances or removing biological components during processing. This could alter their safety as well as the original or biological characteristics that are relevant for their claimed utility. Thus, clinical trials or investigational testing involving humans may be required to assess their safety and effectiveness.

For cells and tissues that are intended to be used in a manner that is not generally accepted to be a homologous use, sponsors must provide evidence to support a claim of homologous use. Health Canada has the authority to require information on relevant characteristics that must be maintained in order for a product to be considered homologous when distributed for a particular indication. Such information may include evidence that shows:

- these characteristics and their contribution to any product claims can be maintained
- the product can effectively perform the proposed function in a safe manner

As noted, cells and tissues are not in the scope of the regulations if they have a systemic effect and depend on their metabolic activity for their main function.

When applied to cells and tissues, a systemic function can be interpreted as "a consequence or effect that is either of a generalized nature or that occurs at a site distant or not related to the location of the cell or tissue". Example: the transplantation of cells that can produce and secrete hormones that act on diverse cells throughout the body. In general, these cells depend on their metabolic activity (for example, the production of hormones and other substances) for their primary function.

In general, cells and tissues that have a systemic effect are excluded from the CTO regulations.

However, islet cells as well as lymphohematopoietic cells that are from bone marrow, peripheral blood and cord blood that have this effect are included in the CTO regulations. These particular cells are included because their safety and effectiveness have been demonstrated through clinical trials and/or established practice. These cells will only be subject to the regulations if they are minimally manipulated. That is, their processing only involves procedures used for pancreas digestion and for purifying specific cell populations from a mixture of cells.

Establishments must fully characterize these products and evaluate their cell preparations to ensure they meet the specifications set for cell number, identity, purity, viability and potency, for example. Note: If these cells are subject to procedures that are considered more than minimal manipulation (for example, *ex-vivo* expansion, cell differentiation or genetic manipulation), they will be subject to other regulations, including the *Food and Drug Regulations* and *Medical Devices Regulations*.

Demineralized bone that's combined with a:

- sterilizing, preserving or storage agent only is considered minimally manipulated and would be considered a cell, tissue or organ
- component other than a sterilizing, preserving or storage agent is not considered a cell, tissue or organ but is regulated as a medical device

Adding a handling component such as calcium carbonate or gelatin, used to modify the structure of the body, results in the product being regulated as a medical device under the *Medical Devices Regulations*.

For questions on the classification of a cell, tissue and organ, please email the Biologic and Radiopharmaceutical Drugs Directorate of Health Canada at brdd-cppic_brdd-cppci@hc-sc.gc.ca.

1.3 Prohibition (section 4)

Transplantation:

4. (1) Subject to sections 40 to 42, no establishment shall transplant a cell, tissue or organ unless it is processed by a registered establishment under these Regulations and determined safe for transplantation.

Importation of cells and tissue:

(2) Subject to sections 40 to 42, no establishment shall import tissue or a cell, other than a lymphohematopoietic cell, unless it is processed by a registered establishment under these regulations and determined safe for transplantation.

Importation of organs and lymphohematopoietic cells:

(3) An establishment may import an organ or lymphohematopoietic cells from an establishment that is not registered.

For imported tissue, evidence of the source establishment's Health Canada registration must be included on the exterior label. Refer to section 31 of the regulations for further guidance on labelling tissues.

The importer must have a system in place to verify that a registered source establishment has processed the products and they are declared safe for transplantation. This should be done before importing from a new source establishment. The products should be assessed periodically to ensure the source establishment continues to meet these requirements.

The term "importation" refers to the importation of cells, tissues and organs from outside Canada. Health Canada does not consider the shipment of these products between different provinces or territories as importation.

1.4 Registration (sections 5 to 14)

Requirement to register:

5. (1) Every establishment must be registered under these regulations, except a retrieval establishment and, subject to subsection (2), a transplant establishment.

Exception:

(2) A transplant establishment that distributes cells, tissues or organs must be registered under these regulations.

Establishments that must register with Health Canada include:

- Canadian establishments responsible for the processing of organs from deceased donors
- Canadian establishments that transplant organs from living donors
- establishments responsible for processing tissues from live and deceased donors
- Canadian establishments that transplant unbanked lymphohematopoietic cells
- Canadian establishments that process and store banked lymphohematopoietic cells
- establishments that distribute cells, tissues and organs within Canada to establishments outside their local health authority
- establishments that import cells, tissues and organs for distribution to establishments within Canada, including those within their own local health authority
- establishments responsible for processing islet cells
- establishments responsible for processing adjunct vessels that are not used immediately during transplantation of the donor organ with which they were retrieved

Establishments that do not have to register with Health Canada include:

- establishments that only retrieve cells, tissues and organs
- establishments that only transplant banked lymphohematopoietic cells
- establishments that only transplant organs from deceased donors
- establishments that only transplant tissues
- foreign establishments that distribute either organs or lymphohematopoietic cells to Canada as per section 4(3)
- foreign establishments that only store or distribute cells, tissues and organs to Canada that they received from a registered source establishment

Application:

6. (1) An application for registration of an establishment must be made in the form established by the Minister, be dated and signed by the medical director or scientific director, and contain all of the following information:

- a. the establishment's name and civic address, and its postal address if different, and the name and telephone number of a person to contact for further information with respect to the application
- b. in the case of an establishment that previously carried out its activities under another name, that other name
- c. a description of the types of cells, tissues and organs that the establishment processes, distributes or imports
- d. a description of the types of processing, distribution or transplantation activities that the establishment carries out or for which it is responsible
- e. the period during which the establishment has been in operation and
- f. a statement dated and signed by the medical director or scientific director that certifies that the establishment is in compliance with these regulations

Information on request:

(2) An establishment must provide the Minister, on written request, with any relevant information necessary to complete the application, by the date specified in the Minister's request.

The registration requirements for cells, tissues and organs:

- provide Health Canada with information on the:
 - identity of the establishments and programs that reside within establishments
 - types of products being processed, distributed or transplanted and the types of activities being carried out
- require registrants to provide assurance to Health Canada that they have met the regulatory requirements for organs and minimally manipulated cells and tissues they import, process or distribute in Canada

Section 6 of the CTO regulations outlines the information that an establishment must provide in its [registration application form](#). This information is mandatory and so must be included in the application form.

Establishments dealing with distinct programs may benefit by submitting a different application form for each program. This would ensure the continuity of other services in the event that 1 program experiences complications. However, separate applications are not required.

Distinct programs include, for example:

- separate live donor and deceased donor programs
- separate transplantation programs for youth and adults
- separate programs with specialization in different types of cells, tissues and organs

Part 1: Type of application

Part 1 of the application form must include the type of registration. If this is the first time an establishment is applying for a registration number, then the establishment must indicate: "Initial application". For change of information applications, make sure to select the correct box and identify the changes clearly.

Part 2: Establishment information

Establishment must indicate:

- the establishment name that will be displayed on their registration certificate
 - the legal name of the establishment
 - may include the program with your establishment name if your organization is very large and specialized (for example, Hospital X- Kidney Transplant Program)
 - program name will appear on the CTO registration certificate
- the Health Canada CTO registration number if it's not your initial application
- the previous name of your establishment if you changed the name but previously carried out activities under this other name

Enter the full civic address of the establishment, including the postal or zip code and the mailing address if it is different from the civic address.

Put down contact information for 2 persons who are directly involved in their program. Make sure the establishment and contact information are accurate and complete, as Health Canada will use this to communicate with your establishment. **Keep this information up to date and submit any changes within 30 days of making the change.**

Complete the additional address section if your establishment has multiple addresses that do not function independently and are part of the same quality management system. Enter the full civic address for these additional addresses. You may add the first 4 additional addresses to the form. Complete a separate annex 1 for each additional address.

Part 3: Source establishment

In part 3 of the registration application form, you must identify whether the establishment is a source establishment. List the cells, tissues and organs they are responsible for as a source establishment, based on the definition of a source establishment:

- for an organ from a deceased donor, the relevant organ donation organization
- for adjunct vessels that are retrieved with an organ and not used immediately in the organ transplantation, the relevant tissue bank
- for an organ from a living donor or lymphohematopoietic cells that are not banked, the relevant transplant establishment
- for tissues or banked lymphohematopoietic cells, the relevant cell or tissue bank
- for islet cells, the establishment that prepares the cells for use in transplantation

Indicate for each of the cells, tissues and organs if the program is for deceased or living donors.

Part 4: Importation and distribution of CTO

Canadian establishments that import or distribute cells, tissues and organs must register with Health Canada. You do not have to register if you only transplant or retrieve these products.

Refer to part 4 of the application form for further instructions if you're a:

- Canadian importer that has their establishment civic address in Canada and obtains CTOs from outside of Canada for distribution to establishments within Canada
- Canadian distributor that has their establishment civic address in Canada and distributes CTOs (for which they are not the source establishment) within Canada to establishments

Part 4 of the registration application form requires you to provide details on the types of CTO your establishment is importing and/or distributing. You also must indicate if you will be storing the cells, tissues and organs and the type of donation (deceased or living donation) for each type of CTO.

You should list the products distributed to Canadian establishments as well as the name and the CTO registration number of the source establishment.

If you're not sure how to classify a product, please contact us by email: brdd-cppic_brdd-cppci@hc-sc.gc.ca.

Limit the information in part 4D to a description of the **types** of processing, distribution or transplantation **activities** that your establishment carries out and that you did not already provide this information in part 4. **We do not require you to provide details of the safety and efficacy of the products for registration. Please do not submit.** We ask that you hold onto this information until we request it. Please provide only a note in part 4D that it's available if needed.

Canadian importers and Canadian distributors should identify the:

- name of the source establishments
- CTO registration number
- type of CTO
- proprietary name of the CTO you're importing or distributing, if applicable

Part 5: Other entity information

"Other entity" refers to an establishment that performs regulated activities such as transmissible disease testing or donor screening. For example, a lab performs infectious disease testing.

Part 6: Statement of compliance

The declaration section of the application contains the following statement:

"I hereby certify that the establishment named in this application is in compliance with the *Safety of Human Cells, Tissues and Organs for Transplantation Regulations*."

The medical director or scientific director must sign and date the declaration in order for the application to be processed. It should not be signed by the CEO, unless the CEO is also the scientific or the medical director. Your establishment can delegate this authority to another individual if this delegation of authority is clearly expressed in your establishment's standard operating procedures (SOP). By signing the declaration, the signatory is attesting that the establishment is in compliance with the CTO regulations. Making false, misleading, inaccurate or incomplete statements is grounds for refusal to issue a registration number, as per section 8 of the regulations.

The declaration of compliance signed by a medical or scientific director assures Health Canada that the establishment acknowledges its responsibilities under the CTO regulations. This provides a level of assurance that:

- cells, tissues and organs imported, processed and/or distributed in Canada meet the safety requirements set out in the CTO regulations
- procedures are in place to protect the public should a problem be identified

The declaration does not preclude us from conducting inspections to verify compliance with the CTO regulations.

The medical director or scientific director is also attesting that the information in the application, including any identified changes, is accurate and complete as required under section 6(1), *Application of the Safety of Human Cells, Tissues and Organs for Transplantation Regulations*.

Send completed applications by email to roeb.cto-dgoral@hc-sc.gc.ca.

To inquire on the status of your establishment's registration, please email us: roeb.cto-dgoral@hc-sc.gc.ca.

Direct all other inquiries to brdd-cppic_brdd-cppci@hc-sc.gc.ca.

Registration number:

7. (1) On review of an application for registration, if the Minister determines that the information provided in the application is complete, the Minister must register the establishment and issue a registration number.

Validity:

(2) Subject to section 9, a registration is valid until December 31 in the year after the year in which the registration number is issued.

All CTO registration numbers expire on **December 31 of the year following the year in which it was issued**. For instance, certificates of registration issued in January 2022 expire on December 31, 2023, as do certificates of registration issued in December 2022.

The establishment must provide the application for renewal to Health Canada's Biological Product Compliance Program before the issued certificate of registration expires. When submitting an application, you must ensure that you have appropriately referenced all relevant changes.

Registration certificates are issued electronically. We will not mail physical copies of the registration certificates to your establishment.

Refusal:

8. The Minister may refuse to register an establishment if he or she has reason to believe that any of the information provided by the establishment in its application is false, misleading, inaccurate or incomplete.

When registration may be cancelled:

9. The Minister may cancel a registration in the following circumstances:

- a. the application for registration contains false or misleading information

- b. the Minister receives a notice under section 13 that states that the establishment has ceased an activity
- c. the establishment has not complied with a request for additional information made under section 14 or
- d. the Minister has reason to believe that the establishment is not in compliance with these Regulations or that the safety of cells, tissues or organs has been or could be compromised

Actions before cancellation:

10. (1) The Minister must take all of the following actions before cancelling a registration:

- a. send a written notice to the establishment that sets out the reasons for the proposed cancellation and specifies the corrective action, if any, that the establishment must take and the time within which it must be taken and
- b. give the establishment an opportunity to be heard in writing with respect to the cancellation

Notice of cancellation:

(2) If the establishment does not carry out the corrective action to the Minister's satisfaction, or does not carry it out within the required time, the Minister must send a notice of cancellation of the registration that includes the reasons for the cancellation and the effective date.

Action by establishment when registration cancelled:

11. On the cancellation of its registration, the establishment must immediately take both of the following steps:

- a. cease carrying out the activities that were authorized by the registration and
- b. notify the establishments to whom it has distributed a cell, tissue or organ or made a donor referral, during the period specified in the notice, of the cancellation, the reasons for the cancellation and the effective date

Cancellation in urgent circumstances:

12. (1) Despite section 10, the Minister may cancel a registration immediately if he or she considers it necessary to do so in order to prevent injury to the health or safety of the public, by giving the establishment a notice of the cancellation in writing that states the reasons for the cancellation.

Request to reconsider:

(2) An establishment may, in writing, request the Minister to reconsider the cancellation.

Opportunity to be heard:

(3) The Minister must, within 45 days after receiving a request for reconsideration, provide the establishment with an opportunity to be heard in writing with respect to the cancellation.

Ongoing requirement to notify Minister:

13. (1) Subject to subsection (2), an establishment must notify the Minister in writing of any change in the information provided in its application for registration, within 30 days after the change is made.

Cessation of activity:

(2) If an establishment ceases to process, distribute or import cells, tissues or organs, it must notify the Minister in writing of that fact, within 90 days after it ceases that activity.

Contents of notice:

(3) The notice must be dated and signed by the medical director or scientific director and include all of the following information:

- a. the establishment's name and civic address, and its postal address if different
- b. the establishment's registration number
- c. the date on which the change or cessation became effective and
- d. in the case of the cessation of an activity, the disposition of the cells, tissues and organs in the establishment's possession

You must inform us in writing of any changes to the information that you provided in your most recent application within 30 calendar days after the change is made.

Complete and submit the [Human Cells, Tissues and Organs \(CTO\) for Transplantation Registration Application Form \(FRM-0171\)](#) along with an accompanying cover letter.

Examples of amendments include:

- changing contact information
- changing the medical or scientific director
- changing your establishment's name or address
- adding or removing an activity
- adding or modifying any CTO information

The notice must be signed and dated by the medical or scientific director (or their designate) and include all of the information stated under subsection 13(3). The information that we require in the notice can be found in the application form. The medical or scientific director must sign and date part 6 of the application form attesting that the establishment is in compliance with the CTO regulations.

Part 7 of the application form contains the information we require to cancel the registration.

Submit changes electronically by emailing us at roeb.cto-dgoral@hc-sc.gc.ca.

For any questions or clarifications, email the [Biological Product Compliance Program](#) at bpcp-pcpb@hc-sc.gc.ca.

Additional information:

14. An establishment must provide the Minister, on written request, with any additional relevant information to demonstrate that the activities it carries out are in compliance with these regulations, by the date specified in the Minister's request.

Under section 14 of the CTO regulations, an establishment must provide us any relevant information that we require to determine if your establishment is in compliance with the CTO regulations.

1.5 Source establishment (section 15)

Responsibility:

15. A source establishment is responsible for the processing of cells, tissues and organs, whether the processing is carried out by the source establishment itself or by another establishment, and for determining whether the cells, tissues and organs are safe for transplantation.

The source establishment is responsible for:

- processing cells, tissues and organs and
- determining the safety of the cell, tissue and organ for transplantation, even if another establishment carried out some or all of the processing activities on behalf of the source establishment

The determination of the source establishment depends on the CTO in question. Source establishment refers to the source of the CTO that has been processed and deemed safe for transplantation.

For organs from a deceased donor, the organ donation organization (ODO) is the source establishment responsible for processing the organs. This reflects current practice as the ODO will typically conduct donor screening and testing or donor suitability assessment. This is a key component in determining if an organ is safe for transplantation.

When an organ is retrieved from a deceased donor, it is common practice to simultaneously retrieve blood vessels from that donor. This aids organ transplantation. Under the CTO regulations, these vessels are referred to as adjunct vessels. They are subject to the same regulatory requirements as organs.

If the adjunct vessels are not used immediately in the transplantation of the organ with which they were retrieved, the establishment that is responsible for storing and then distributing the adjunct vessels must register as a source establishment. The source establishment must ensure that adjunct vessels intended for transplantation are stored and documented appropriately.

The source establishment must follow the requirements for organs in the CTO regulations since the adjunct vessels continue to be regulated as organs under the regulations and are not regulated as tissues. The source establishment is responsible for receiving and reviewing the relevant organ donor suitability assessment information, including the questionnaire, test

results and physical exam results, before transplantation. This is very important in cases where the vessels are transplanted in an individual other than the original organ recipient.

Health Canada recommends that organ transplant establishments keep records of any adjunct vessels that are stored for future use, regardless of whether the transplant establishment:

- is registered as the source establishment for the stored vessels **or**
- has transferred this responsibility to another party, such as an affiliated tissue bank

We also recommend that organ transplant establishments let source establishments know if and where they store adjunct vessels that are not used during the surgical procedure of the organ recipient. Doing so ensures that adjunct vessels can be appropriately identified and either quarantined or traced to a recipient in the event that any adverse reactions are reported in organ recipients who received an organ from the donor of the adjunct vessels.

The source establishment must also:

- ensure that the vessels are used within a scientifically based predetermined number of days and for recording to which establishment they distributed the vessels
- record information to identify the recipient of vessels used within the source establishment

In some cases, adjunct vessels will need to be released before the source establishment has reviewed the documentation. Under these conditions and if appropriate, the transplanting physician may authorize the exceptional distribution of these vessels (sections 40 to 42 of the CTO regulations).

Where exceptional distribution is applied to an organ of a donor, the exceptional distribution process does not have to be repeated for using the adjunct vessels retrieved from that same donor if the person receiving the organ and the vessels and if the reason for the exceptional distribution are the same. However, the documentation requirements of sections 40 to 42 of the regulations must still be met.

For organ donation from a living donor, the source establishment responsible for processing the organ is the relevant transplant establishment, which will need to register. The same is true for allogeneic (for use in another individual) lymphohematopoietic cell donations that are not banked.

The transplant establishment is still the responsible source establishment regardless of which establishment assesses the donor or which organization looks after matching the donor and the recipient. For example, the transplant establishment is still considered the source establishment for living donor kidney transplants that involve a donor who travels from the program where the donor workup and testing took place or that involve an organ that is shipped for transplantation.

The transplant establishment is responsible for obtaining and reviewing the appropriate documentation and determining the safety of the organ. The transplant establishment does

not, however, need to repeat the donor screening and testing if it deems the existing results acceptable.

Health Canada recommends that the living donor organ donation and transplantation community work together to develop standardized SOPs and questionnaires. This help to ensure consistency of donor screening and testing practices among the different organizations involved.

We recognize that for unrelated lymphohematopoietic cell donations, the different activities carried out by establishments may be on a continuum. In this case the source establishment is the transplant establishment, and will need to register. For example, even if a stem cell registry or a retrieval establishment initiates donor testing, the transplant establishment is responsible for reviewing these results and determining the safety of the donation.

For all tissues and lymphohematopoietic cells that are banked, the tissue or cell bank is the source establishment responsible for processing and the safety of the cells and tissues. This bank may be either a specific or a comprehensive tissue or cell bank.

Note: The term "banked" in this context does not refer to cells and tissues that are obtained from a source establishment and stored by the end user for a period of time before use in transplantation. Under the CTO regulations, "banked" cells and tissues are those for which all other processing activities (with the exception of final labelling) have been completed, are stored by the **source establishment** in their inventory and are available for distribution and transplantation.

For lymphohematopoietic cells collected from bone marrow or peripheral blood, any storage of the cells is not considered banking if the donation is reserved for treating a designated recipient.

Example illustrating the definition of source establishment in the case of a multiple tissue/organ donor, where there may be more than 1 source establishment for a given donor (where bone, ocular tissue, kidney and liver were to be retrieved from a donor):

As per the definition in the CTO regulations, the organ donation organization (ODO) would be the source establishment responsible for processing and the safety of the organs. The bone and eye bank would be responsible, respectively, for processing and the safety of the bone and ocular tissue. Similarly, if the bone and ocular tissue were retrieved for a comprehensive tissue bank, the tissue bank would be responsible for processing and the safety of the tissues.

Note: Being the source establishment in 1 circumstance for a particular CTO does not mean the establishment is the source establishment for all CTOs that it handles or processes.

A good example of this is an ODO. An ODO is the source establishment for organs from deceased donors. While it may be involved in tissue donation, it is **not** the source establishment for tissues.

Each establishment must rely on the CTO regulations and their definitions, along with this guidance document, to determine its responsibilities for the safety and processing of CTOs

under these regulations. All establishments involved in processing the CTO should agree on which establishment will function as the source establishment.

Note that composite tissues, which are vascularized composite allografts consisting of multiple tissue types (for example, a full face or hand transplant), can meet the definition of a tissue or an organ under the CTO regulations. It is up to the source establishment to determine which set of regulatory provisions is most appropriate for their circumstances. Provided the relevant regulatory provisions relating to either tissues or organs are met, the organ or tissue source establishment that's registered as per Section 5 of the regulations may distribute composite tissue (without using exceptional distribution).

1.6 Processing (sections 16 to 27)

General

The extent of the responsibility of source establishments for the processing and safety of CTOs under section 15 of the regulations is determined by the meaning of the term "processing". Processing (defined in section 1 of the regulations) includes:

- donor screening
- donor testing
- donor suitability assessment
- retrieval, except for organs and islet cells
- testing and measurements performed on the cells, tissues or organs after they're retrieved
- preparation for use in transplantation, except for organs
- preservation
- quarantine
- banking
- packaging and labelling

Each of these activities is described in more detail under the following applicable regulatory requirements. Information about donor suitability assessment, including donor screening and testing, is organized as follows:

- section 18 contains the general requirements for all CTOs except lymphohematopoietic cells
- sections 20, 21 and 22 contain additional requirements for tissues, ocular tissues and organs
- section 23 contains all the requirements for lymphohematopoietic cells

The responsibility of source establishments for the activities described applies whether or not the source establishment carries out the activities itself, or if they are performed by another establishment on behalf of the source establishment.

Documented evidence:

16. An establishment must have documented evidence that demonstrates that the activities, processes and technical procedures that it uses in processing cells, tissues and organs will consistently lead to the expected results.

For these regulations, documented evidence refers to activities, processes and technical procedures that:

- the establishment has validated or
- have been established in standards developed by recognized professional organizations, based on established practice or
- are supported by information available in the scientific literature

When pooling permitted:

17. An establishment may only pool cells, tissues or organs from different donors during processing to create a therapeutic dose for a single recipient.

Donor Suitability Assessment

Requirements for cell, tissue and organ donors:

18. In assessing the suitability of a donor of cells, tissues or organs, except a donor of lymphohematopoietic cells, an establishment must perform all of the following steps:

- a. obtain the donor information and history in accordance with sections 12.2 and 12.3 of the general standard
- b. determine that the donor is not unsuitable to donate on the basis of the contraindications or exclusion criteria set out in section 13.1.3 of the general standard and in Annex E to that standard
- c. perform a physical examination of the donor in accordance with section 13.2 of the general standard
- d. perform appropriate and effective tests for the diseases or disease agents specified in section 14.2.6 of the general standard

Section 18 applies to all cells, tissues and organs with the exception of lymphohematopoietic cells. Refer to section 23 for donor suitability requirements for lymphohematopoietic cells.

Donor suitability assessment

Donor suitability assessment (section 12.2 of the general standard), which is intended to elicit risk factors, is based on the donor's medical and social history, clinical status, physical examination, tests and, if performed, an autopsy. Documentation of this assessment must include all the elements specified in section 12.3 of the general standard.

Where an autopsy is to be performed and it's determined the integrity of the CTO will be compromised before the report is completed, you do not need to wait for the final report of

the autopsy results. Rather, the presumed cause of death and other pertinent preliminary autopsy findings should be taken into consideration and documented.

Donor screening

Donor screening is 1 component of donor suitability assessment. It's done to elicit general health information and identify risk factors (such as infectious disease risks) that could impact the safety of the CTO.

This risk assessment is based on the donor's medical and social history, clinical status, physical examination, tests and, if performed, an autopsy. The donor's medical and social history and clinical status can be obtained through a donor interview and a review of the donor's medical records or charts. The interview must be conducted using a medical/sexual/social history questionnaire that includes the applicable contraindications/exclusion criteria and other relevant questions required under the CTO regulations. The interview should be documented in the form of a checklist where the response/outcome for each criterion is recorded.

If the donor is deceased or cannot participate in the interview, at least 1 person who can provide the necessary information may be interviewed. This person could be:

- the donor's next of kin or nearest available relative
- someone who has a relationship with the donor
 - such as a caretaker, friend, partner
- a member of the donor's household
- the donor's primary physician

The interview should take place in person or by telephone.

An establishment must develop and maintain SOPs for all steps performed during donor screening. This includes the steps involved in conducting the donor medical/sexual/social history interview and administering the donor screening questionnaire(s). If a questionnaire developed by a professional organization is to be used, an establishment must review the questionnaire to determine if it meets all the requirements of the CTO regulations for donor screening.

Screening of living donors should be done as close to the time of retrieval as feasible. If more than 1 month has elapsed since the donor screening questionnaire was completed and the retrieval has not yet occurred, we recommend that you review the living donor screening results with the donor as close to the time of retrieval as feasible to see if any information has changed. An abbreviated donor screening questionnaire is acceptable provided it addresses all the necessary exclusion criteria.

When a potential donor is part of the medical assistance in dying (MAID) program, the information communicated by the living potential donor may be considered part of the donor screening assessment. However, you must verify that the information is still true within the necessary timeframes for donation and that the assessment is completed in accordance with the establishment's SOP.

The donor suitability requirements that apply to living donors apply for conscious and competent donors. Once organ retrieval begins, the requirements for deceased donors apply.

When screening donors under 11 years of age, you should collect answers to screening questions used to determine high risk for HIV, HBV or HCV in a manner that is appropriate to the donor's age. This should be described in the establishment's SOP.

Contraindications or exclusion criteria

The conditions and behaviours set out in section 13.1.3 and Annex E of the general standard may increase the risk that a donor may have and/or could potentially transmit an infectious disease to the recipient. Donors are to be excluded from donating a CTO on the basis of these contraindications/exclusion criteria. The exception is when exceptional distribution is used (for more information, consult sections 40 to 42 of the CTO regulations).

Note that recent changes to Annex E in the 2022 edition of the CSA Z900.1 standard include the following:

- the deferral period for persons who report nonmedical intravenous, intramuscular or subcutaneous injection of drugs has been reduced from 5 years to 12 months
- the deferral period for persons who have engaged in sex in exchange for money or drugs has been reduced from 5 years to 12 months
- the deferral for persons with a history of intranasal cocaine use has been expanded to include all drug use for nonmedical reasons

Examples of prion-related disease that are described as exclusion criteria in section 13.1.3 of the general standard include, among others:

- Creutzfeldt-Jakob disease
- variant Creutzfeldt-Jakob disease
- other transmissible spongiform encephalopathies

Examples of degenerative neurologic disorders of viral or unknown etiology that are described in section 13.1.3 of the general standard include, among others:

- Parkinson's disease
- subacute sclerosing panencephalitis
- progressive multifocal leukoencephalopathy
- amyotrophic lateral sclerosis (Lou Gehrig's disease)

Section 13.1.3 of the general standard states:

"A donor shall be excluded if any of the following contraindications apply: persons with a history of infection with HIV, clinically active HCV or clinically active HBV."

This clause has been amended to refer to persons with a history of clinically active HBV or HCV. The amendment clarifies that where there was a suspicion of hepatitis in the donor's medical history (outside of the current donor suitability assessment) it may be possible to requalify the donor if the validity of this information is in question. Requalification can be done by performing the necessary donor screening and testing required under the CTO regulations. We also recommend that you perform nucleic acid testing (NAT) under these circumstances as a precaution.

Section 13.1.3 (f) of the general standard excludes donors "with active encephalitis or meningitis of infectious or unknown etiology". Undiagnosed meningitis or encephalitis has been linked to high rates of transmission of infection to organ recipients, which can lead to significant morbidity and mortality.

The Organ Procurement and Transplantation Network, together with the United Network for Organ Sharing, has developed a guidance document for evaluating potential organ donors for meningoencephalitis during the donor screening process.

Learn more:

- [Ad Hoc Disease Transmission Advisory Committee's \(DTAC\) practical guidance](#)

Other infections may also exclude the donation of a CTO, if the infection would pose a significant risk to the recipient if transmitted.

Physical examination

Before a CTO is donated (with the exception of lymphohematopoietic cells, which are dealt with under section 23) from a potential donor, a qualified person must perform the physical examination. This must be done in accordance with the establishment's SOP, which must comply with section 13.2 of the general standard.

When a potential donor is part of the medical assistance in dying (MAID) program, a physical exam of the conscious and competent potential donor may be considered part of the donor screening assessment. However, the information must be verified as true within the necessary timeframes for donation and the assessment must be completed in accordance with the establishment's SOP. Any mandatory living donor tests for which results are not obtained must result in the organs being distributed under exceptional distribution only.

For conscious and competent patients, the physical examination must be performed within 30 days of the scheduled date of the medical assistance in dying procedure or when life-sustaining measures are withdrawn.

Deceased donors

In the case of a deceased donor, the mandatory physical examination includes a recent antemortem or postmortem physical examination and a directed physical examination. It may include a limited autopsy, if performed. The directed examination should include any of the following applicable items that would help determine evidence of high-risk behaviour

Along with information gathered as part of the donor medical/social history, the following physical evidence is used to evaluate the donor's risk of having a transmissible disease. While not all of the identified risk factors will necessarily lead to the donor being excluded, the information could help in clinical decision-making.

The following physical evidence are examples that may be associated with the presence of a transmissible disease and should be assessed in a directed physical examination performed on all potential deceased CTO donors:

- signs of sexually transmitted diseases, such as:
 - genital ulcerative disease
 - herpes simplex
 - syphilis
 - chancroid
- physical evidence of nonmedical percutaneous drug use, such as:
 - needle tracks, including an examination of tattoos as they may cover needle tracks
- physical evidence of tattooing, ear piercing or body piercing
- unexplained lymphadenopathy (swollen lymph nodes)
- oral thrush
- blue or purple spots consistent with Kaposi's sarcoma
- unexplained jaundice/icterus or hepatomegaly
 - hepatomegaly may not be apparent in a physical examination unless an autopsy is performed
- physical evidence of sepsis, such as:
 - unexplained generalized rash
- large scab consistent with recent smallpox immunization
- eczema vaccinatum
- generalized vesicular rash (generalized vaccinia)
- severely necrotic lesion consistent with vaccinia necrosum
- corneal scarring consistent with vaccinia keratitis

It's very rare that you will encounter signs of physical evidence associated with a recent smallpox (vaccinia) immunization. However, you could encounter these signs in:

- those who perform laboratory work involving orthopoxviruses
- military personnel who have served or will serve overseas
- first responders who are specially trained to respond to threats of bioterrorism

A physical examination of skin donors must include documentation of findings and conditions that may affect the quality or quantity of skin retrieved.

For deceased donors, a full visualization of the external body shall be performed. If full visualization is not feasible, the assessment shall be deemed incomplete.

Living donors

In the case of a potential living donor, all donors must be given a physical exam. The exam must look for evidence of:

- high-risk behaviour, such as:
 - needle tracks or other signs of injection drug use
- signs of bacterial, fungal, parasitic or viral infections of clinical significance **and**
- signs of malignancy

Physical exams should be done as close to the time of retrieval as is reasonable and practical. We recommend within 30 days of the anticipated date of retrieval.

If the retrieval of the organ or tissue is postponed, the source establishment will need to determine if a repeat physical exam or a limited repeat physical exam is warranted.

If an examination of the donor was already done for other reasons (for example, to determine if donation is safe for the donor), the findings from this previous examination can be reviewed and documented in the donor's records. However, the exam must have been performed within the recommended timeline.

In general, the findings of a physical exam performed for other reasons may not be reported in a manner that specifically addresses the risk factors of interest. In this case, a new physical exam must be performed to confirm or rule out **potential** risk factors that are identified during the medical/social history review. The new physical exam must assess any physical evidence that could indicate high-risk behaviour associated with the presence of a transmissible disease.

For donations of amniotic membrane tissue, a surrogate physical examination of the mother must be performed and the results must be documented.

Standard operating procedures (SOPs)

An establishment must have SOPs describing how to conduct physical examinations of donors.

Donor testing

General requirements

Donor testing may include:

- laboratory tests for transmissible disease agents, such as:
 - HIV
 - hepatitis B virus (HBV)
 - hepatitis C virus (HCV)
- tests to determine the donor's blood type, such as:
 - ABO group
 - Rh type
- procedures to evaluate or provide information on the CTO itself

The following guidance for donor testing focuses on laboratory tests for the various transmissible disease agents that apply to CTO donors.

For information on donors of lymphohematopoietic cells, refer to section 23 of the CTO regulations.

Timeframe for collecting specimens

Health Canada considers the timeframes in Table 1 to be appropriate and effective.

Ideally, specimens for infectious disease testing for all CTO donors should be collected as close to the donation as possible.

Table 1: Timeframe for collecting specimens for testing HIV-1, HIV-2, HCV and HBV and diseases or disease agents specified in the infectious disease testing requirements of the applicable subset standards

Type of CTO	Type of testing required	Timeframe
Tissue from deceased infant donor ≤ 28 days old and who had no obvious potential exposure to a blood born pathogen after birth	serological screening tests plus NAT for HIV-1 and HCV performed on the person who carries the infant donor to delivery	Refer to the sub-section on deceased tissue donor test specimen collection timeframes
Tissue from deceased infant donor > 28 days old*	serological screening tests plus NAT for HIV-1 and HCV performed on infant donor	Refer to the sub-section on deceased tissue donor test specimen collection timeframes
Tissue from deceased donor*	serological screening tests performed on donor plus NAT for HIV-1 and HCV	Refer to the sub-section on deceased tissue donor test specimen collection timeframes
Tissue from live donor	serological screening tests performed on donor	within 7 days before retrieval or 7 days after retrieval
deceased organ donor	serological diagnostic or screening tests performed on donor	as close to the time of donation as possible, with tests performed on the most recent sample for which donor identity and sample quality can be ensured

live organ donor (including conscious and competent donors)	serological diagnostic or screening tests performed on donor	within 30 days before donation and it is recommended to retest at the time of donation
organ from infant donor ≤ 28 days old	serological diagnostic or screening tests performed on the person who carries the infant donor to delivery	within 7 days before or at the time of donation
organ from infant donor > 28 days old but < 18 months or who was breastfed in the last 12 months	serological diagnostic or screening tests performed on the infant donor as well as the person who carries the infant donor to delivery, unless HIV-1 and HCV NAT is performed on the infant, in which case all tests should only be performed on the infant	within 7 days before or at the time of donation

* While antemortem or postmortem specimens are acceptable, we recommend that a pre-mortem specimen be used, if available. This specimen is likely to be less hemolyzed, and excessive hemolysis can interfere with the test results. The donor may have received fluid infusions shortly before dying as well, which would dilute the plasma enough to affect test results.

Note: NAT for HIV-1 and HCV is mandatory for tissue (including ocular tissue) from deceased donors. It is not necessary for tissue from living donors if the 180 quarantine and donor retesting protocol is followed (outlined in section 17.2 of the tissue standard).

Establishments must have SOPs that specify the timeframes for collecting blood specimens from donors of each type of CTO.

For deceased donors, blood testing results are acceptable if sample collection takes place within 7 days before the time of cardiac death or cross clamping of the aorta.

For cadaveric donors (non-heart beating donors), blood testing results are acceptable if sample collection takes place:

- a) as specified in the relevant sections of the package inserts of test kits approved for cadaveric specimens
- b) within 24 hours after the time of death in cases where the test kit package insert does not specify a timeframe and the validation section of the package insert does not specify the hours after death within which the specimens were collected or
- c) up to 24 hours after the time of death in situations where the package insert specifies a collection timeframe of less than 24 hours, if in this instance, the establishment that

made the decision to extend the collection time up to 24 hours has a documented risk-based rationale approved by the medical director available to support the decision

Note: The documentation under item c) is to support the approval of the overall procedure relevant to the collection timeframes for deceased donor samples at the establishment. The supporting information used in the document may include, among other things:

- medical reasons (including risk of not releasing the tissue)
- supply considerations
- previous relevant experience at the establishment
- input from the establishment's own or other infectious disease-testing labs
- evidence or supporting rationale from available literature or a detailed scientific document

Infectious disease testing

All source establishments are responsible for infectious disease testing, including testing that another establishment carries out on its behalf. They must have appropriate documentation (such as SOPs, agreements, contracts or audit reports) to support that infectious disease testing is performed in accordance with the following:

- Testing shall be performed by a laboratory that meets applicable requirements of the authority having jurisdiction over that laboratory.
- The tests for infectious diseases or disease agents that could lead to the exclusion of the donor must be performed using test kits that are licensed as required in sections 25 and 26 of the regulations. The tests for infectious diseases or disease agents that do not lead to donor exclusion (for example, CMV), must be performed using test kits that are licensed as required in section 25.
- The testing laboratories must follow the test kit manufacturer's instructions for:
 - collecting, handling and storing blood specimens
 - timeframe within which samples must be tested, if applicable
 - procedure for testing
 - interpreting test results

Interpreting infectious disease test results

The terms used by test kit manufacturers for interpreting serological test results are determined, in part, by the testing algorithms used.

In general, the initial serological screening test is performed using a single blood sample. A nonreactive sample is considered a negative test result and further testing is not required.

In contrast, a reactive sample is considered initially reactive instead of positive because the:

- sample has to be retested in duplicate using the same test but not necessarily the same lot
- results are considered repeatedly reactive if either 1 of the 2 replicates is reactive

These 2 additional steps are necessary to achieve the final outcome ("positive" or "negative") of the test kit in the event that a sample is initially reactive.

Note: This testing algorithm is an example only. Establishments must always apply the specific testing algorithm indicated in the test kit's instructions for use.

Also, some test kit manufacturers may recommend confirmatory or supplemental testing with a different test kit to confirm the results of the first test kit. While confirmatory testing is necessary for patient diagnosis, it should not be considered for screening donors because false negative confirmatory test results cannot be ruled out. Thus, in these circumstances, donors must still be excluded regardless of the confirmatory test results.

In cases where confirmatory testing is performed for patient diagnosis, establishments that use third-party testing labs must ensure that they are given the results of the initial test kit so they may determine donor eligibility.

In addition, instead of using the term "repeatedly reactive" for the final outcome of a particular screening or diagnostic test, some test kit manufacturers use the terms "reactive" or "positive".

In this guidance document:

- A **negative** test result means the **final outcome** in which the test kit manufacturer determines the test specimen is nonreactive.
- A **positive** test result means the **final outcome** in which the test kit manufacturer determines the test specimen is "reactive", "repeatedly reactive" or "positive".
- A **confirmed positive** test result means the outcome of a confirmatory or supplemental test performed using a **different test kit**, in which the tested specimen is determined to be reactive.

A determination of donor eligibility includes the interpretation of the following infectious disease test results:

- **HIV-1 and 2, HBV, HCV and HTLV-I and II:** The CTO must not be released for transplantation if the donor's specimen is positive for any of the infectious disease markers specified in this document. Where additional tests are done to confirm or supplement the positive test results (for example, for donor or next-of-kin notification), the CTO must not be released for transplantation, unless the exceptional distribution provisions are met, even if the confirmatory or supplemental test results are negative.
- **Syphilis:** The CTO may be released for transplantation if the donor's blood sample is positive using a nontreponemal test, but negative using a treponemal-specific confirmatory assay. If establishments decide to use a treponemal-specific assay for syphilis as the test of record, the CTO must not be released for transplantation if the donor's specimen is positive unless the exceptional distribution provisions are met. This is because a positive treponemal-specific test identifies both recent and remote or treated syphilis infections. While a nontreponemal test can be performed to rule out a recent infection, false negative results cannot be ruled out. Thus, appropriate testing algorithms must be developed to resolve this issue.
- **Cytomegalovirus (CMV) and Epstein-Barr virus (EBV):** The cells or organ may be released for distribution if a donor's blood sample is positive or the test results are pending. It is not necessary to use exceptional distribution under these circumstances.

The test results for these infectious agents may be important in selecting the cells or organ for specific patients and can impact recipient monitoring protocols. These results must be communicated to the transplant physicians.

- **Toxoplasmosis tests for heart donors:** Donor eligibility is not determined through test results. Therefore, the tests may be performed retrospectively. However, the test results are important for monitoring heart recipients and must be communicated to the transplant physicians when they become available. Note: Positive results that are received after transplantation are not considered an error/accident under the CTO regulations unless the test was initially reported as negative and then the results were positive.
- **Establishment performs additional tests that are not mandatory (for example, nucleic acid testing (NAT) for HIV-1, HCV, HBV and WNV for organ donors) or obtains such test results for a shared donor from another establishment:** The results must be taken into consideration when determining donor eligibility if they are available before the CTO is released. If a positive result is obtained for a disease or disease agent that is a contraindication to donation, the donor should be excluded, unless exceptional distribution is used.

If a donor's specimen tests positive for HIV, HBV or HCV using a required serological test but is negative using NAT, the CTO cannot be distributed, unless done under exceptional distribution.

Note: Exceptional distribution may be used if the donor specimen is repeatedly reactive or positive for markers of infectious disease agents. More information on exceptional distribution can be found in sections 40 to 42 of the CTO regulations.

Results of all tests, including optional tests, must be included in the donor records. Establishments must have SOPs for interpreting and handling test results, including communicating results to transplant physicians or to establishments to which the CTO are distributed. Procedures must also be established for handling the results of tests that become available after the CTO has been released for distribution. Such procedures must include notification of transplant physicians or establishments to which the CTO is distributed.

Archived samples

The CTO regulations do not require that samples be collected for archiving as this has no impact on the safety of CTOs that meet current regulatory requirements. However, cell, tissue, plasma or serum samples from each donor should be archived for retrospective testing of donors of cells and tissues that are still in inventory when new tests are adopted to screen donors for existing or emerging pathogens.

Retrospective testing is based on the degree of safety enhancement afforded by the new tests, as well as the availability of tests that are appropriately validated or approved under the *Medical Devices Regulations* (MDR) for testing frozen specimens. Health Canada will inform CTO establishments if retrospective testing is required.

If establishments choose to archive samples, they must have SOPs for collecting and storing samples being archived. Samples must be stored frozen and should be kept for at least 5 years.

Establishments must have documentation to show that the archived samples are stored at the appropriate temperature.

Tests that are considered appropriate and effective

Mandatory testing:

All CTO donors must be tested for the infectious disease agents listed in the sections of the general standard referenced in the CTO regulations, using appropriate and effective tests. We consider a test to be appropriate and effective if it is:

- licensed to detect the infectious disease agent or marker in accordance with the licensing requirements specified in sections 25 and 26 of the CTO regulations
- used in accordance with the test kit manufacturer's instructions
- used to detect an infectious disease marker that is relevant at the time that testing is done
 - appropriate infectious disease markers are provided below
 - also refer to the complete list of all required and recommended tests

Section 14.2.6.1 of the general standard:

- specifies the infectious disease agents for which testing must be done for all CTO donors
- requires additional tests specified in the subset standards

The following sections list infectious disease markers that are considered appropriate and effective for detecting donors infected with the disease agents listed in the general and subset standards. This list may be revised when new infectious disease tests become licensed or when new information necessitates an amendment.

Health Canada considers tests for the following infectious diseases markers to be appropriate and effective in order to comply with section 14.2.6.1 of the general standard:

- antibodies to the human immunodeficiency virus, types 1 and type 2 (anti-HIV-1 and anti-HIV-2)
- hepatitis B surface antigen (HBsAg)
- total antibody to hepatitis B core antigen (anti-HBc, IgG and IgM)
- antibodies to hepatitis C virus (anti-HCV)
- nucleic acid testing (NAT) for detecting HIV-1 in deceased tissue donors and ocular tissue donors
- nucleic acid testing (NAT) for detecting HCV in deceased tissue donors and ocular tissue donors

The person who carries the infant donor to delivery and donor must be tested for infectious disease agents for infant donors under the age of 18 months or who were breastfed at any time during the 12 months before donation. This is to address vertical transmission of infectious agents to the donor (section 14.2.6.2 of the general standard).

The following exceptions apply:

- For donors who are 28 days old or younger and who had no obvious potential exposure to a blood-borne pathogen after birth, surrogate testing of the person who carries the infant donor to delivery is to be performed.
- For donors who are 29 days old or older, if nucleic acid testing is used for detecting HIV-1 and HCV, all testing in 14.2.6.1 of the general standard is to be performed on the infant donor.

Establishments must have SOPs that describe which infectious disease tests must be performed and when surrogate testing is required for infant donors.

Recommended testing:

Living organ donors should also be tested for HIV-1 and HCV using NAT.

NAT should be performed on organ donors (living and deceased) where it is clinically indicated. An example is if a decision is made to use exceptional distribution for a CTO from a donor with a history of high-risk behaviour and a negative serological test for HIV and HCV.

Organ, islet cell and tissue donors (including ocular tissue donors) should be tested for WNV using a test kit that is licensed to detect viral nucleic acid. Testing could be done seasonally if specific procedures are in place to determine:

- the timeframes for seasonal testing
- other circumstances when testing for WNV may be required outside of these timeframes, such as:
 - when a donor has travelled to an endemic area

Given the transient nature of WNV viremia, Health Canada recommends that blood samples be tested on the day of donation or as close to the time of donation as is feasible. WNV testing turnaround times should be considered. As with other infectious diseases, donors could become infected with WNV after sample collection but before donation if the samples are collected before donation. Additional screening and/or testing samples collected on the day of donation could address this risk.

Health Canada has licensed a test kit to detect WNV ribonucleic acid in plasma specimens from both living and deceased donors. (Our Medical Devices Directorate is the Canadian federal regulator responsible for licensing in accordance with the MDR.)

[Medical devices active licence listing \(MDALL\)](#)

Health Canada has a database of licensed Class II, Class III and Class IV medical devices for sale in Canada. You can verify the licensing information of test kits approved for donor screening by visiting the [medical devices active licence listing \(MDALL\)](#) web page and then using the “active licence search” function.

Note that test kits approved for donor screening are licensed as class 4 devices, but not all class 4 test kits are necessarily approved for donor screening.

As of 2024, the names of all newly authorized infectious disease tests kits approved for donor screening in MDALL will not indicate that they are approved for donor screening. However, all newly authorized infectious disease tests kits will have published regulatory decision summaries that can be used to verify whether new test kits are licensed for donor screening.

Plasma dilution algorithm:

19. In assessing the suitability of a donor, an establishment must apply a plasma dilution algorithm if a donor pre-transfusion or pre-infusion blood sample is unavailable.

Blood transfusion or infusion of intravenous fluid could dilute the donor's blood. This could lead to:

- a decrease in concentration of circulating antigens and antibodies
- false negative results for infectious disease tests

Testing must be performed on a suitable blood sample (as defined by the establishment's SOPs) that's collected as close to the time of retrieval as possible. Testing should be done on the **most recent pre-transfusion/infusion blood sample** for which identity and quality can be ensured. If no suitable pre-transfusion/infusion blood sample is available, benchmarks for **plasma dilution** shall be applied to determine whether the degree of plasma dilution is or is not sufficient to affect test results. If no suitable pre-transfusion/infusion blood sample and no other suitable specimen is available for testing based on the results of the plasma dilution algorithm, this constitutes a contraindication to donation.

Establishments must have SOPs that describe situations that could result in plasma dilution, as well as the collection of pre-transfusion/infusion samples.

Health Canada does not provide guidance on the types of infused fluids to consider when calculating plasma dilution. We also do not recommend or review plasma dilution algorithms. Establishments must develop their own SOPs that outline their plasma dilution algorithms. Algorithms must be validated, established in standards developed by recognized professional organizations or supported by information available in the scientific literature.

Additional exclusion criteria for tissue donors:

20. In assessing the suitability of a tissue donor, except an ocular tissue donor, an establishment must perform both of the following steps:

- a. determine that the donor is not unsuitable to donate on the basis of the contraindications or exclusion criteria set out in section 13.1.2 of the tissue standard
- b. perform appropriate and effective tests for the diseases or disease agents specified in section 14.2.6 of the tissue standard

Contraindications/exclusionary criteria

In addition to the exclusion criteria of section 13.1.3 of the general standard, donors are excluded from donating tissues on the basis of the exclusionary criteria in section 13.1.2 of the tissue standard.

Note: One new exclusion criteria has been added to section 13.1.2 of the tissue standard in the 2022 edition:

- persons with a medical diagnosis of WNV infection in the past 120 days

Tests that are considered appropriate and effective

Mandatory testing:

In addition to tests for the disease or disease agents specified in section 14.2.6 of the general standard, Health Canada considers the following tests are appropriate and effective for testing tissue donors in order to comply with section 14.2.6 of the tissue standard:

- serologic assays for detecting antibodies to human T-lymphotropic virus type I and type II (anti-HTLV-I and HTLV-II) for donors of viable, leukocyte-rich tissue
- non-treponemal or treponemal-specific serologic assays for detecting syphilis

Please refer to Table 1 for timeframes for collecting specimens.

Note: Health Canada will permit exemptions from the requirement to perform NAT for fresh tissue grafts that cannot be stored for a sufficient period of time to allow for receiving nucleic acid test (NAT) results before transplantation. Establishments that wish to exempt fresh tissue grafts from NAT must make sure their SOPs:

- contain the appropriate documentation to support the exemption
- describe which tissues are exempt from NAT, the rationale for exemption and any circumstances under which NAT may or may not be used

In these cases, fresh tissue grafts can be distributed without having to use exceptional distribution when NAT is not performed.

Recommended testing:

Donors of tissues not considered leukocyte-rich should also be tested for HTLV-I and HTLV-II.

Tissue that is not considered leukocyte-rich includes, among others:

- skin
- bone
- sclera
- corneas
- tendons
- cartilage
- ligaments
- amniotic tissue
- osteoarticular allograft tissue

Additional exclusion criteria for ocular tissue donors:

21. In assessing the suitability of an ocular tissue donor, an establishment must determine that the donor is not unsuitable to donate on the basis of the contraindications or exclusion criteria set out in sections 13.1.3 to 13.1.6 of the ocular standard.

Contraindications/exclusionary criteria

In addition to the exclusion criteria of section 13.1.3 of the general standard, donors must be excluded from donating ocular tissue on the basis of the exclusionary criteria in sections 13.1.3 to sections 13.1.6 of the ocular standard. Note that 13.1.3 (h) and (i) of the ocular standard are not intended to exclude the use of healthy tissue from a donor with intrinsic eye disease or a congenital or acquired disorder that only affects 1 eye. The contraindication only applies to the affected eye.

Note: One new exclusion criteria has been added to section 13.1.3 of the ocular standard in the 2022 edition:

- persons with a medical diagnosis of WNV infection in the past 120 days

Eligibility based on HTLV and syphilis testing

Ocular tissue may be used for transplantation without having to use exceptional distribution (subject to approval by the source establishment's medical director) when testing for:

- anti-HTLV-I or anti-HTLV-II on an ocular tissue donor (for example, for the purposes of organ donation from the same donor) and such tests are positive
- syphilis on an ocular tissue donor (for example, for the purposes of organ donation from the same donor) and such tests are positive

Additional requirements for organ and islet cell donors:

22. (1) In assessing the suitability of an organ or islet cell donor, an establishment must perform all of the following steps:

- a. obtain the donor information and history in accordance with sections 12.2.2.3, 12.2.2.4, 12.2.3.4 and 12.2.3.7 of the organ standard
- b. determine that the donor is not unsuitable to donate on the basis of the contraindications or exclusion criteria set out in section 13.2.2 of the organ standard
- c. perform the tests specified in sections 14.1.2 and 14.3.2 of the organ standard
- d. perform appropriate and effective tests for the diseases or disease agents specified in sections 14.2.6.3 and 14.2.6.6 of the organ standard

Exception for imported organs:

(2) Despite subsection (1), in the case of an imported organ, the transplant establishment need only have the following:

- a. documentation of the donor suitability assessment according to the requirements of the jurisdiction where the assessment was performed
- b. documentation that the tests specified in sections 14.1.2 and 14.3.2 of the organ standard have been performed
- c. documentation that appropriate and effective tests for the diseases or disease agents specified in sections 14.2.6.3 and 14.2.6.6 of the organ standard have been performed
- d. in the case of those of the tests for the diseases or disease agents specified in section 14.2.6.3 of the organ standard that must be performed before transplantation and the blood group test for ABO, a copy of the test results

Donor information and history

Section 12.2.2.3 of the organ standard requires that a donor history be taken for travel or residence outside the United States and Canada. Establishments should work with an infectious disease specialist to develop SOPs for the risk of infectious diseases that can be acquired abroad.

Travel history and timeframe of travel history along with donor symptoms, medical records and findings of the physical exam can help rule out active infections that could be acquired abroad. Travel-related diseases to consider include malaria, chagas, Zika, Ebola, dengue fever, strongyloides and West Nile virus.

Cases of donor allergies transferred to recipients have been reported for hematopoietic cell transplantation and solid organ transplantation, including potentially fatal allergies to nuts, seafood, penicillin and latex.

To address this concern, the medical social history requirements in section 12.2.2.3 of the organ standard have been amended to include information on life-threatening donor allergies. This information must be in the donor history, so that transplant establishments can take

measures to address the possibility that the recipient could develop an allergy from the transplant. This is especially if the cause of the donor's death was due to an anaphylactic reaction from being exposed to an allergen.

To address the current medication requirement, establishments must assess the donor for prescribed medications and other current medications, including over-the-counter drugs or natural health products.

Contraindications/exclusionary criteria

In addition to the exclusion criteria of section 13.1.3 of the general standard, donors must be excluded from donating organs and islet cells on the basis of the exclusionary criteria in section 13.2.2 of the organ standard.

The donor's surgeon must assess the physical quality of the organ(s) being donated. The surgeon must document any abnormality or concern, such as the presence of an unsuspected infection or malignancy, and notify transplanting programs immediately.

Tests that are considered appropriate and effective

Mandatory testing:

In addition to tests for the disease or disease agents specified in section 14.2.6 of the general standard, Health Canada considers the following tests to be appropriate and effective for testing organ and islet cells donors (to comply with section 14.2.6.3 of the organ standard):

- serologic assays for detecting antibodies to human T-lymphotropic virus type I and type II (anti-HTLV-I and HTLV-II)
- serologic assays for detecting antibodies to toxoplasmosis for **heart** donors,
 - may be performed retrospectively by testing for antibody to toxoplasmosis in the donor's serum using a medically acceptable test, such as enzyme-linked immunoassay
- non-treponemal or treponemal-specific serologic assays for detecting syphilis
- serologic assays for detecting IgG antibodies to cytomegalovirus (anti-CMV IgG or anti-CMV (total))
- serologic assays for detecting antibodies to Epstein-Barr virus that can detect recent and past EBV infections (as determined acceptable by the source establishment and described in their SOPs)
 - see recommended testing for EBV below for additional guidance on EBV testing

Note: Results of the tests for CMV, EBV and toxoplasmosis may be reported following organ distribution.

Please refer to [Table 1](#) for timeframes for specimen collection.

Recommended testing:

Testing for WNV nucleic acid (WNV NAT) is recommended for organ and islet cell donors (section 14.2.6.4 of the organ standard). Anti-CMV IgM testing is also recommended.

An anti-viral capsid antigen IgG (anti-VCA IgG) test is recommended for detecting EBV and could be supplemented with an anti-VCA IgM test to enhance detection of recent infections. Anti-EBV nuclear antigen (anti-EBNA IgG) IgG tests should be supplemented with appropriate EBV tests for enhanced early detection of EBV infection, as EBNA IgG antibodies may not be detected in recently infected individuals.

Living organ donors should also be tested for HIV-1 and HCV using NAT, if available. In particular, NAT should be performed on organ donors (living and deceased) where it's clinically indicated. An example is if a decision is made to use exceptional distribution for a CTO from a donor with a history of high-risk behaviour and a negative serological test for HIV and HCV.

Physical exam

For conscious and competent patients, the physical examination must be performed within 30 days from the scheduled date of the medical assistance in dying procedure or when life-sustaining measures were withdrawn.

Requirements for imported organs

For imported organs from deceased donors, the source establishment would be the foreign ODO.

In some cases:

- the foreign ODO may deal directly with the Canadian transplant establishment, which would not have to register as an importer since it's only importing for use in its own establishment
- a Canadian ODO may be involved in the process, but acting on behalf of the transplant establishment as a facilitator

The transplant establishment and the Canadian ODO must clearly identify their respective roles and responsibilities for imported organs within their SOPs. This includes identifying the information that the ODO must obtain on behalf of the transplant establishment. This is necessary for the establishment to meet the requirements of subsection 22(2) of the CTO regulations.

Section 22(2) of the regulations provides an exception to organ standard provisions referenced in Section 22(1). Note: Section 22(2) does not exempt imported organs from general standard requirements referenced in Section 18 of the regulations, including ensuring that the testing requirements in section 14.2.6 of the general standard have been completed.

Requirements for lymphohematopoietic cells:

23. (1) In assessing the suitability of a donor of lymphohematopoietic cells, an establishment must perform all of the following steps:

- a. obtain the donor information and history in accordance with sections 12.2.2.2 and 12.2.2.3 of the lymphohematopoietic standard

- b. perform a physical examination of the donor in accordance with section 13.2 of the lymphohematopoietic standard
- c. determine that the donor is not unsuitable to donate on the basis of the contraindications or exclusion criteria set out in section 13.1.3 of the lymphohematopoietic standard
- d. perform the tests specified in section 12.2.2.4 of the lymphohematopoietic standard
- e. perform appropriate and effective tests for the diseases or disease agents specified in section 14.2.3 of the lymphohematopoietic standard

Exception for imported lymphohematopoietic cells:

(2) Despite subsection (1), in the case of imported lymphohematopoietic cells, the source establishment must:

- a. have documentation of the donor suitability assessment
- b. perform the tests specified in section 12.2.2.4 of the lymphohematopoietic standard
- c. perform appropriate and effective tests for the diseases or disease agents specified in section 14.2.3 of the lymphohematopoietic standard
- d. determine that the donor is not unsuitable to donate on the basis of the exclusion criteria set out in section 13.1.3.4 of the lymphohematopoietic standard

In the case of cord blood, the infant is considered the donor. However, transmissible disease testing and a physical exam must be performed on the person who carries the infant donor to delivery (referred to as surrogate testing).

Assessment of donor suitability

An assessment of donor suitability (section 12.2 of the lymphohematopoietic standard) is done to identify risk factors. In general, the assessment is based on medical and social history, clinical status, physical examination and tests.

Documentation of this assessment:

- must include all the elements specified in section 12.2.2.3 of the lymphohematopoietic standard
- should include all the elements in section 12.3 of the general standards, as specified in section 12.3 of the lymphohematopoietic standard

Donor screening

Donor screening is one component of donor suitability assessment, It's done to gather general health information and identify risk factors (such as infectious disease risks) that may impact the safety of the lymphohematopoietic cells.

The risk assessment is based on the donor's medical and social history, clinical status, physical examination and tests. Medical and social history and clinical status information can be obtained through a donor interview and a review of the donor's medical records or charts. A medical/sexual/social history questionnaire that includes the applicable

contraindications/exclusion criteria and other relevant questions should be used to interview a donor. The responses should be documented in the form of a checklist so the response/outcome for each criterion can be recorded.

For a child donor, at least 1 knowledgeable person, such as the donor's parents or legal guardian, should provide the required information. The interview should be done in person or by telephone.

Donor screening should be done as close to the time of retrieval as feasible. The donor screening results should be reviewed with the donor as close to the time of retrieval as feasible, to determine if any information has changed, if:

- more than 1 month has elapsed since the donor screening questionnaire was completed
- retrieval has not yet occurred

In these cases, an abbreviated donor screening questionnaire is acceptable provided it addresses all the necessary exclusion criteria.

An establishment must develop and maintain SOPs for all donor screening steps, including those governing the donor medical/sexual/social history interview and the donor screening questionnaire(s). If a questionnaire developed by a professional organization is used, the establishment must make sure it meets the requirements of the CTO regulations for donor screening.

Cases of donor allergies transferred to recipients have been reported for lymphohematopoietic cell transplantation and solid organ transplantation, including potentially fatal allergies to nuts, seafood, penicillin and latex. We have amended the medical social history requirements in section 12.2.2.3.1 of the lymphohematopoietic cell standard to include information on life-threatening donor allergies. Except for cord blood, establishments must capture this information as part of the donor history to address the possibility that the recipient could develop an allergy as a result of the transplant.

Documentation of a donor's medical and social history must include any travel or residence outside the United States and Canada. Establishments should develop SOPs that address travel-related diseases, such as malaria, chagas, Zika, Ebola, dengue and West Nile virus.

Travel history and timeframe of travel history as well as donor symptoms, medical records and physical exam results can help rule out active infections that could be acquired abroad.

Unless tested for WNV, a donor's travel history in the past 56 days must also be obtained to ascertain if the donor had travelled to WNV-endemic areas, including those within Canada. This is to comply with sections 14.2.3 (d) (i) and (ii) of the lymphohematopoietic cell standard. A travel history within Canada is necessary when:

- WNV is potentially transmissible

- the establishment is not going to test for WNV for donors who reside in regions of Canada that are not considered endemic for WNV

Contraindications/exclusion criteria

The conditions and behaviours set out in section 13.1.3 of the lymphohematopoietic standard and Annex E of the general standard may increase the risk that a donor may have and/or could potentially transmit an infectious disease to the recipient. Donors are thus excluded from donating lymphohematopoietic cells on the basis of these contraindications/exclusion criteria, except where exceptional distribution is used. For more information, refer to sections 40 to 42 of the CTO regulations.

A first-degree relative is the genetic mother, father, sibling or child of the recipient. Anyone who is not a first-degree relative must comply with the requirements of section 13.1.3.2 of the lymphohematopoietic standard. Under this section, all allogeneic donors, including cord blood donors, who are not first-degree relatives of the recipient must be screened according to the criteria specified in Annex E of the general standard.

Section 13.1.3 of the lymphohematopoietic standard gives examples of diseases that are in the exclusion criteria:

- neurological diseases of unestablished etiology such as multiple sclerosis, Alzheimer's, Parkinson's and amyotrophic lateral sclerosis (Lou Gehrig's disease)
- prion-related diseases such as Creutzfeldt-Jakob disease, variant Creutzfeldt-Jakob disease and other transmissible spongiform encephalopathies

For cord blood donors, first-degree relatives include their genetic mother, father and siblings.

Section 13.1.3.3 of the lymphohematopoietic standard lists additional exclusion criteria that apply to cord blood donors, unless the risk has been excluded through either biological parent testing, donor testing or follow-up.

A cord blood unit shall not be accepted for unrelated allogeneic use if there's a first-degree relative of the infant donor with:

- a known history of a malignant disease with an established heritable component
- an established heritable predisposition to cancer
- a genetic disorder that might be transmissible to the recipient

Examples of malignant disease with a heritable component or a genetic disorder:

- cancer or leukemia that are associated with germline mutations (such as RUNX1 acute leukemia, germline p53 mutations)
- select red blood cell diseases
- select white blood cell diseases
- select platelet diseases
- select metabolic/storage diseases
- select immune deficiencies/dysregulatory diseases

If the genetic or medical history of a donor's first-degree biological relative is unknown or unobtainable, the cord blood unit is not accepted as safe for transplantation. This includes cases where the donor was conceived from a sperm or egg donation, or both.

These units could, however, be collected and banked for release under exceptional distribution.

For allogeneic donations taking place outside of Canada, donors must be assessed and accepted by the collection facility and documentation of suitability must be provided to the transplant establishment. A donor from outside of Canada must be excluded if they have HIV, HBV or HCV.

Physical examination

Donors must undergo a physical examination for evidence of:

- certain high-risk behaviours (such as needle tracks or other signs of injection drug use)
- bacterial, fungal, parasitic or viral infections of clinical significance
- malignancy

Physical exams should be done as close to the time of retrieval as is reasonable and practical (within 30 days of the anticipate date of cell retrieval). If retrieval is postponed, the source establishment will need to determine whether a repeat physical exam or a limited repeat physical exam is warranted. Such decisions can be delegated to the physician at the collection centre.

If the donor was examined before for other reasons, such as to determine if donation is safe for the donor, the findings can be reviewed and documented in the donor's records in lieu of a new physical examination. However, this exam must have been done within the recommended timeline. Such decisions can be delegated to the physician of the collection centre.

In the case of cord blood, a surrogate physical examination of the person who carries the infant donor to delivery must be performed and the results documented. If a physical examination was previously performed while the person was pregnant, the findings can be reviewed and documented in the donor's records in lieu of a new physical examination. However, this exam must have been done within the recommended timeline.

An establishment must have SOPs describing how the physical exam of the donor is to be conducted.

Donor testing

General requirements

Donor testing includes a number of tests, such as:

- lab tests for transmissible disease agents, such as HIV, HBV and HCV
- tests to determine the donor's blood type (ABO group and Rh type) and HLA type
- procedures to evaluate or provide information on the lymphohematopoietic cells

The following guidance on donor testing focuses on HLA typing and lab tests for the various transmissible disease agents applicable to lymphohematopoietic cell donors.

Sections 12.2.2.4.2 (e) and (f) of the lymphohematopoietic standard stipulates that cord blood HLA typing must be done at the time of banking and before release for unrelated allogeneic cord blood. Cord blood that's reserved for and restricted to potential allogeneic use in a relative of the donor only needs to be HLA-typed before release. In this case, a second HLA typing to confirm the identity of the unit is not required if the initial HLA typing is done after a recipient has been identified and the HLA typing is of sufficient resolution.

Units that have had confirmatory HLA typing performed on a contiguous segment at some point post-freeze do not require repeat confirmatory testing before being released from the cord blood bank.

Timeframe for collecting specimens

Infectious disease tests must be performed using blood specimens taken within 7 days before or 7 days following collection of cord blood and within 30 days before other donations are collected (for example, lymphohematopoietic cells derived from bone marrow and peripheral blood. This is stipulated in subsection 12.2.2.4 of the lymphohematopoietic standard.

Collecting specimens within 30 days before the donation makes it possible to determine donor eligibility within the timeframe required for the recipient to initiate myeloablative chemotherapy. If collections from the same donor take place more than 30 days apart, the donor must be retested for infectious disease markers, unless a previously positive test result has been documented.

Health Canada considers the timeframes in Table 2 are appropriate and effective.

Table 2: Timeframe for collecting specimens for testing diseases or disease agents specified in the infectious disease testing requirements of the lymphohematopoietic standard

Type of CTO	Type of testing required	Timeframe
Cord blood	serological screening tests and NAT for HIV-1 and HCV performed on the person who carries the infant donor to delivery	within 7 days before or 7 days following collection
	WNV NAT performed on the person who carries the infant donor to delivery	Within 7 days before or 7 days following collection*
lymphohematopoietic cells (excluding cord blood)	serological screening tests performed on donor	within 30 days before collection (12.2.2.4.1)

	WNV NAT on donor	within 30 days before collection (12.2.2.4.1)
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*Given the transient nature of WNV viremia, blood samples should be tested on the day of donation or as close to the time of donation as feasible, taking into consideration WNV testing turnaround times. If this is not possible for cord blood donors and samples are collected after the donation, a WNV IgM test should be done along with the WNV NAT to detect recent WNV infection in donors with negative WNV NAT results. As with other infectious diseases, donors could become infected with WNV after sample collection but before donation if the samples are collected before donation. Additional screening and/or testing the samples on the day of donation could address this.

Establishments must have SOPs that specify the timeframes for collecting blood specimens from donors of each type of lymphohematopoietic cells.

Infectious disease testing

All source establishments are responsible for infectious disease testing, including testing that another establishment carries out on its behalf. They must have appropriate documentation (such as SOPs, agreements, contracts or audit reports) to support that testing was done as follows:

- Testing shall be performed by a laboratory that meets the applicable requirements of the authority having jurisdiction over that laboratory.
- Tests for infectious diseases or disease agents that could lead to the exclusion of the donor (such as diseases or disease agents that are exclusion criteria under the CTO regulations) must be performed using test kits that are licensed as required in sections 25 and 26 of the regulations. Tests for infectious diseases or disease agents that do not lead to donor exclusion must be performed using test kits that are licensed as required in section 25.
- Testing laboratories must follow the test kit manufacturer's instructions for:
 - collecting, handling and storing blood specimen
 - the timeframe within which samples must be tested, if applicable
 - the procedure for testing
 - interpreting test results

Interpreting infectious disease test results

The terms used by test kit manufacturers for interpreting serological test results are determined, in part, by the testing algorithms used. In general, the initial serological screening test is done using a single blood sample. A nonreactive sample is considered a negative test result and further testing is not required. A reactive sample is considered initially reactive instead of positive because the:

- sample has to be retested in duplicate using the same test but not necessarily the same lot and
- results are considered repeatedly reactive if either 1 of the 2 replicates is reactive

These 2 additional steps are necessary to achieve the final outcome ("positive" or "negative") in the event that a sample is initially reactive. Note: This testing algorithm is only an example. Establishments must always apply the specific testing algorithm indicated in the test kit's instructions for use.

Note also that some test kit manufacturers may also recommend confirmatory or supplemental testing with a different test kit to confirm the results of the first test kit. Confirmatory testing is necessary for patient diagnosis, but not for donor screening because false negative confirmatory test results cannot be ruled out. In these circumstances, donors must still be excluded regardless of the confirmatory test results.

Establishments that use third-party testing labs must make sure they are given the initial test kit results in cases where confirmatory testing is done for patient diagnosis. This will help them determine donor eligibility appropriately.

Instead of using "repeatedly reactive" for the final outcome of a particular screening or diagnostic test, some test kit manufacturers use "reactive" or "positive".

In this guidance document:

- A negative test result is the final outcome in which the test specimen is determined to be nonreactive by the test kit manufacturer.
- A positive test result is the final outcome in which the test specimen is determined to be "reactive", "repeatedly reactive" or "positive" according to the testing algorithms proposed by the test kit manufacturer.
- A confirmed positive test result is the outcome of a confirmatory or supplemental test performed using a different test kit, in which the tested specimen is determined to be reactive.

Donor eligibility determination must include an interpretation of the infectious disease test results as outlined:

- **HIV-1 and 2, HBV, HCV and HTLV-I and II:** Lymphohematopoietic cells shall not be released for transplantation if the donor's specimen is positive for any of the infectious disease markers specified in this document. Where additional tests are performed to confirm or supplement the positive test results (such as for notifying donors or next-of-kin), lymphohematopoietic cells must not be released for transplantation, unless the exceptional distribution provisions are met, even if the confirmatory or supplemental test results are negative.
- **Syphilis testing:** Lymphohematopoietic cells may be released for transplantation if the donor's blood sample is positive using a nontreponemal test, but negative using a treponemal-specific confirmatory assay. Note: If establishments use a treponemal-specific assay for syphilis as the test of record, the lymphohematopoietic cells must not

be released for transplantation if the donor's specimen is positive unless the exceptional distribution provisions are met. This is because a positive treponemal-specific test identifies both recent and remote or treated syphilis infections. While a nontreponemal test can rule out a recent infection, false negative results cannot be ruled out. Thus, appropriate testing algorithms must be developed to resolve this issue.

- **Additional tests that are not mandatory (such as NAT for HIV-1 or HCV for unbanked cells):** The results must be considered when determining donor eligibility if they are available before the lymphohematopoietic cells are released.
- **Cytomegalovirus (CMV) and Epstein-Barr virus (EBV):** Cells may be released for distribution if a donor's blood sample is positive or the test results are pending. It's not necessary to use exceptional distribution under these circumstances. The test results for these infectious agents may be important when selecting cells for specific patients and can impact recipient monitoring protocols. These results must be communicated to the transplant physicians.

If a donor's specimen tests positive for HIV, HBV or HCV using a required serological test but is negative using NAT, the cells cannot be distributed, unless under exceptional distribution.

Note: In exceptional circumstances, cells from the donor who is repeatedly reactive or positive for the markers of infectious disease agents, may be used under exceptional distribution. For more information on exceptional distribution, consult sections 40 to 42 of the CTO regulations.

Results of all tests, including optional tests, must be included in the donor records.

Establishments must have SOPs for interpreting and handling all test results, including communicating these results to transplant physicians or to establishments to which the lymphohematopoietic cells are distributed. There must also be procedures for handling the results of optional tests that become available after the lymphohematopoietic cells have been released for distribution. The procedures must include notifying transplant physicians or establishments to which the lymphohematopoietic cells are distributed.

Archived samples

The CTO regulations do not require that samples be collected for archiving. This has no impact on the safety of lymphohematopoietic cells that meet current regulatory requirements. We recommend archiving cell, tissue, plasma or serum samples from each donor for retrospective testing of donors of lymphohematopoietic cells that are inventoried when new tests are adopted for screening donors for existing or emerging pathogens.

When to conduct retrospective testing will be based on the:

- degree of safety enhancement the new tests provide
- availability of tests that are appropriately validated or approved under the *Medical Devices Regulations* for testing frozen specimens

Health Canada will inform CTO establishments if retrospective testing is required.

Establishments that choose to archive samples must have SOPs for collecting and storing samples. Samples must be stored frozen and should be kept for at least 5 years. Establishments

must also have documentation to show the samples are kept at the appropriate temperature while in storage.

Tests that are considered appropriate and effective

Mandatory testing

Donors of lymphohematopoietic cells must be tested for the infectious disease agents listed in section 14.2.3 of the lymphohematopoietic standard, using appropriate and effective tests. A test is considered appropriate and effective if it is:

- licensed for detecting the infectious disease agent or marker in accordance with the licensing requirements specified in sections 25 and 26 of the CTO regulations
- used in accordance with the test kit manufacturer's instructions
- used for detecting an infectious disease marker that's relevant at the time testing is performed

A list of appropriate infectious disease markers is provided below. Consult the complete [list of required and recommended tests](#) as well. This list may be revised when new infectious disease tests become licensed or when new information necessitates an amendment.

Health Canada considers the following tests are appropriate and effective for testing lymphohematopoietic cell donors to comply with section 14.2.3 of the lymphohematopoietic standard:

- serologic assays for detecting antibodies to the human immunodeficiency virus, types 1 and type 2 (anti-HIV-1 and anti-HIV-2)
- serologic assays for detecting hepatitis B surface antigen (HBsAg)
- serologic assays for detecting total antibody to hepatitis B core antigen (anti-HBc, IgG and IgM)
- serologic assays for detecting antibodies to hepatitis C virus (anti-HCV)
- serologic assays for detecting antibodies to human T-lymphotropic virus type I and type II (anti-HTLV-I and anti-HTLV-II)
- serologic assays for detecting IgG antibodies to cytomegalovirus [anti-CMV IgG or anti-CMV (total)]
- non-treponemal or treponemal-specific serologic assays for detecting syphilis
- assays for detecting West Nile virus (WNV) nucleic acid (if the donation falls within the timeframes for seasonal testing there are other circumstances that would lead to testing outside of those timeframes (for example, if a donor has travelled to an area where WNV is endemic)
- nucleic acid testing (NAT) for detecting HIV-1 for banked lymphohematopoietic cell donations (cord blood donations)
- nucleic acid testing (NAT) for detecting HCV for banked lymphohematopoietic cell donations (cord blood donations)

For infant donors, the person who carries the infant donor to delivery must be tested for infectious disease agents to address vertical transmission of infectious agents to a donor who:

- is under the age of 18 months old **or**
- was breastfeeding at any time during the 12 months before donation

This is in accordance with section 14.2.6.2 of the general standard.

However, the person who carries the infant donor to delivery of an infant donor who is 29 days or older does not need to be tested for infectious disease agents if testing the infant donor includes the serological tests listed as well as NAT for HIV-1 and HCV.

In the case of donated cord blood, only surrogate testing of the person who carries the infant donor to delivery is required.

The establishments must have SOPs that describe which infectious disease tests must be performed and when surrogate testing is required for infant donors.

Lymphohematopoietic cell donors must be tested for WNV using a test kit that has been licensed to detect viral nucleic acid. Testing could be done seasonally if specific procedures are in place to determine:

- the timeframes for seasonal testing **and**
- other circumstances when testing for WNV may be required outside of these timeframes
 - for example, when a donor has travelled to an endemic area

Health Canada has licensed a test kit for detecting WNV ribonucleic acid in plasma specimens from both living and deceased donors.

The minimum donor testing requirements stated in section 12.2.2.4 of the lymphohematopoietic standard must be met before transplantation.

Recommended testing:

Donors of unbanked lymphohematopoietic cells should also be tested for HIV-1 and HCV using NAT, if available. NAT should be performed in circumstances where it's clinically indicated: for example, for exceptional distribution for lymphohematopoietic cells from a donor with a history of high-risk behaviour and a negative serological test for HIV and HCV.

Health Canada's Medical Devices Directorate is the Canadian federal regulator responsible for licensing in accordance with the *Medical Devices Regulations* (MDR). The [medical devices active licence listing \(MDALL\)](#) database lists licensed Class II, Class III and Class IV medical devices for sale in Canada. Select "active licence search" to find a device by company name, licence name device name, company ID or licence number.

Retrieval interval for tissues:

24. An establishment that retrieves tissue from a deceased donor must carry out the retrieval within the scientifically based maximum interval between the cardiac asystole of the donor and the retrieval of the tissue.

The maximum interval between the cardiac asystole of the donor and the retrieval of the tissue is considered scientifically based if it meets 1 or more of the following criteria:

- the maximum interval between the cardiac asystole of the donor and the retrieval of the tissue has been established in standards developed by recognized professional organizations, based on established practice
- data is available in the scientific literature to support the maximum interval between the cardiac asystole of the donor and the retrieval of the tissue
- the maximum interval between the cardiac asystole of the donor and the retrieval of the tissue has been validated by the establishment

Licensed diagnostic devices:

25. (1) Subject to subsection (2), *in vitro* diagnostic devices that are used by an establishment in the testing of donor blood for transmissible disease agents or markers under these regulations must be licensed either:

- a. in Canada, if the testing is performed in Canada
- b. in Canada or the United States, if the testing is performed outside Canada

Exception for lymphohematopoietic cells:

(2) In the case of lymphohematopoietic cells that are imported into Canada for transplantation into a specific recipient, the *in vitro* diagnostic devices may be licensed in Canada or any other jurisdiction.

Under subsection 25(1) of the CTO regulations, the *in vitro* diagnostic devices that an establishment uses to test donors of CTO for transmissible diseases or disease agents must be licensed in Canada, if the testing is done in Canada. If the testing is done outside of Canada, the *in vitro* diagnostic devices must be licensed either in Canada or the United States.

Subsection 25(2) makes an exception for lymphohematopoietic cells that are imported into Canada for transplantation into a specific recipient. In this case, the *in vitro* diagnostic devices used in donor testing may be licensed in Canada or any other jurisdiction.

Health Canada's Medical Devices Directorate is the Canadian federal regulator responsible for licensing in accordance with the MDR.

The [medical devices active licence listing \(MDALL\)](#) database lists licensed Class II, Class III and Class IV medical devices for sale in Canada.

***In vitro* diagnostic devices for cells and tissues:**

26. (1) In the case of cells and tissues, *in vitro* diagnostic devices that are used by an establishment in the testing of donor blood for transmissible disease agents or markers under these regulations must be licensed for screening donors.

Exception for syphilis:

(2) Despite subsection (1), *in vitro* diagnostic devices that are used in the testing of donor blood for syphilis may be licensed either for diagnosis or screening donors.

Donor screening test kits are licensed based on investigational testing in a population with a low disease prevalence (such as healthy blood donors). The emphasis is on test sensitivity.

Investigational testing of test kits that are licensed for diagnosis is performed in a symptomatic population. The emphasis is on test specificity. For this reason, test kits that are licensed for donor screening are considered more appropriate for screening CTO donors.

Tests that are licensed for screening donors (as opposed to tests that are licensed for diagnostic purposes) are not required for detecting the presence of a disease or disease agent in a donor that's not considered a contraindication to donation. An example is Cytomegalovirus (CMV) testing of lymphohematopoietic cell donors.

For this reason, we are amending section 26 (1) to only require assays that are licensed for screening donors for diseases or disease agents that are exclusion criteria to donation under the CTO regulations. This will allow establishments to use assays that are either licensed for diagnostic purposes or for screening donors when testing donors for diseases or disease agents that are not exclusion criteria under the regulations.

In the interim, we will assign a low priority to enforcement actions for establishments that are using assays licensed for diagnostic purposes when testing donors for diseases or disease agents that are not exclusion criteria under the regulations. Establishments will not be required to use exceptional distribution in these circumstances.

For tissues and cells, with the exception of islet cells, diagnostic devices that an establishment uses to test for diseases or disease agents that are exclusion criteria under the CTO regulations must be licensed for screening donors. Infectious disease test kits used for organ donors may be licensed for either screening donors or for diagnosis, as the timeframes for organ transplantation don't always permit the use of screening tests. The CTO regulations also indicate that test kits licensed for diagnosis can be used to test for syphilis.

Infectious disease tests are also licensed for different types of specimens. The test kit manufacturers provide instructions for how to use each test kit in the package insert.

For CTO donations, a test may be licensed for testing blood specimens obtained from live donors (for example, the blood specimen is obtained while the donor's heart is still beating) or from cadaveric donors (for example, the blood specimen is obtained after the donor's heart stops beating). For specimens obtained after the donor's heart stops beating, establishments should use a test that's licensed for cadaveric specimens, if such tests are available where the test is being performed.

Bacteriological testing of tissues:

27. An establishment that retrieves tissue, except ocular tissue, must perform bacteriological testing in accordance with section 14.3 of the tissue standard, except for section 14.3.2.8.

Source establishment requirements

The source establishment must ensure that laboratories performing microbial testing meet the applicable requirements of the authorities having jurisdiction. A copy of the laboratory's most recent certificate of accreditation would fulfill this requirement.

Testing establishment requirements

Laboratories must ensure that microbial testing is performed in accordance with validated procedures by qualified staff and that the test results are documented in the donor's record. Methods, materials and equipment must be suitable for their intended use. Lot numbers, expiry dates and other relevant information should be recorded.

Indirect or direct sampling methods may be used to obtain microbial culture test samples. Samples may be collected from each individual tissue or obtained using a sampling strategy that represents all the tissues received from a particular donor.

Indirect sampling is done by swabbing or extracting fluid. Direct sampling is done by placing samples of tissue directly into growth media.

Quality control (QC) testing must be performed for any transport medium prepared in-house to ensure both aerobic and anaerobic organisms stay viable. Growth media prepared in-house must be subject to QC testing to ensure it is sterile and can support the growth of aerobic and anaerobic organisms.

Tissue sampling and test methods must be evaluated for sensitivity and found to be appropriate and effective for each tissue type recovered and processed.

All testing methods and protocols must be documented in the establishment's standard operating procedures (SOPs).

Consult the following when reviewing or updating established microbiological sampling plans and microbiological test methods:

- [AATB guidance document: Microbiological process validation and surveillance program](#) (American Association of Tissue Banks)
- [CBS leading evidence based practice guidelines for tissue recovery, microbial sampling, processing of musculoskeletal tissue, processing of cardiac tissue and processing of skin tissue](#) (Canadian Blood Services)

1.7 Packaging and labelling (sections 28 to 33)

Packaging materials

28. An establishment that packages cells, tissues or organs must ensure that it uses appropriate packaging materials that are free from damage and capable of maintaining the integrity of the cells, tissues and organs.

An establishment must have documented evidence that the packaging materials can maintain the integrity of the CTO. This evidence must be available upon request. Evidence could consist of specification sheets, certificates of analysis (COAs) or manufacturer's package inserts describing the packaging material.

The packaging materials must also be compatible with the CTO to prevent any interactions that may cause the package to degrade or chemicals from the packaging to be absorbed by the CTO. Only use packaging materials that have been assessed and released by quality assurance (QA) personnel or by a designated alternate. The QA personnel or designated alternate must approve any changes to the packaging materials before they are used. Materials that are outdated or rejected should be kept apart until they can be disposed. This should be recorded. All packaging materials must be visually inspected.

Language requirement

29. All of the information that is required by these regulations to appear on a label or package insert must be in either English or French.

Cells, except islet cells:

30. (1) An establishment that distributes cells, except islet cells, must ensure that all of the applicable information, as indicated by an "X", set out in the table to this subsection is provided on the interior label, in the package insert and on the exterior label.

Pancreas and islet cells:

(2) An establishment that distributes a pancreas for islet cell transplantation, or islet cells, must ensure that all of the applicable information, as indicated by an "X", set out in the table to this subsection is provided on the interior label, in the package insert and on the exterior label.

The interior label is the label that is affixed to the interior package, which is the innermost package of a cell, tissue or organ that has a non-sterile exterior.

The package insert is the document that the source establishment prepares to accompany a cell, tissue or organ.

The exterior label is the label that is affixed to the exterior package, which is the outermost package in which a cell, tissue or organ is delivered, transported or shipped in.

Table to subsection 30(1): Labelling requirements for cells, except islet cells

Item	Column 1 Required information	Column 2			Column 3			Column 4		
		From retrieval establishment to transplant establishment			From retrieval establishment to cell bank			From cell bank to any other establishment		
		Interi or label	Packa ge insert	Exteri or label	Interi or label	Packa ge insert	Exteri or label	Interi or label	Packa ge insert	Exteri or label
Information about donor and cell										
1.	Name of cell	yes	yes	n/a	yes	yes	n/a	yes	yes	n/a
2.	Description of cell	n/a	yes	n/a	n/a	yes	n/a	n/a	yes	n/a
3.	Donor identification code, clearly labelled as such	yes	yes	n/a	n/a	n/a	n/a	yes	yes	n/a
4.	Information capable of identifying the donor	n/a	n/a	n/a	yes	yes	n/a	n/a	n/a	n/a
5.	Donor assessment record	n/a	n/a	n/a	n/a	yes	n/a	n/a	n/a	n/a
6.	ABO group and Rh factor of donor, if applicable	yes	yes	n/a	yes	yes	n/a	yes	yes	n/a
7.	The hazard pictogram entitled "Biohazardous infectious material" set out in Schedule 3 of the <i>Hazardous Products Regulations</i> , if applicable	yes	n/a	yes	yes	n/a	yes	yes	n/a	yes
Retrieval information										
8.	Date, time and time	n/a	yes	n/a	n/a	yes	n/a	n/a	n/a	n/a

	zone of retrieval									
9.	Information specific to retrieval procedure	n/a	yes	n/a	n/a	yes	n/a	n/a	n/a	n/a
Processing information										
10.	Name of anticoagulant and other additive, if applicable	n/a	yes	n/a	n/a	yes	n/a	n/a	yes	n/a
11.	Statement "For autologous use only", if applicable	yes	yes	n/a	yes	yes	n/a	yes	yes	n/a
Information for transplant establishment										
12.	Statement that the cell has been declared safe for transplantation	n/a	n/a	n/a	n/a	n/a	n/a	n/a	yes	n/a
13.	Statement "For exceptional distribution", if applicable	n/a	yes	n/a	n/a	n/a	n/a	n/a	yes	n/a
14.	If applicable, the reasons for exceptional distribution and a statement of how the cell does not meet	n/a	yes	n/a	n/a	n/a	n/a	n/a	yes	n/a

	the requirements of these Regulations									
15.	Instructions on how to report errors, accidents and adverse reactions	n/a	n/a	n/a	n/a	n/a	n/a	n/a	yes	n/a
16.	Expiry date and time, if applicable	n/a	n/a	n/a	n/a	n/a	n/a	yes	yes	n/a
Establishment information										
17.	Name of retrieval establishment, its civic address and contact information	n/a	yes	yes	n/a	yes	yes	n/a	n/a	n/a
18.	Name of source establishment, its civic address and contact information	n/a	yes	yes	n/a	yes	yes	n/a	yes	yes
19.	Registration number of source establishment, clearly labelled as such	n/a	yes	yes	n/a	n/a	n/a	n/a	yes	yes
20.	Name of transplant establishment, if known, its civic address and	n/a	n/a	yes	n/a	n/a	n/a	n/a	n/a	yes

	contact information									
Storage information										
21.	Statement “Human cells for transplant”	n/a	n/a	yes	n/a	n/a	yes	n/a	n/a	yes
22.	Handling instructions for storage and for storage during transportation	n/a	n/a	yes	n/a	n/a	yes	n/a	n/a	yes

n/a: not applicable

Table to subsection 30(2): Labelling requirements for pancreas and islet cells

Item	Column 1 Required information	Column 2			Column 3		
		Pancreas: From retrieval establishment to source establishment			Islet cells: From source establishment to any other establishment		
		Interior label	Package insert	Exterior label	Interior label	Package insert	Exterior label
Information about donor and organ or islet cells							
1.	Name of organ or cells, as applicable	yes	yes	n/a	yes	yes	n/a
2.	Description of organ or cells, as applicable	n/a	yes	n/a	yes	yes	n/a
3.	Donor identification code, clearly labelled as such	n/a	n/a	n/a	yes	yes	n/a
4.	Information capable of identifying the donor	yes	yes	n/a	n/a	n/a	n/a

5.	Donor assessment record	n/a	yes	n/a	n/a	n/a	n/a
6.	ABO group and Rh factor of donor, if applicable	yes	yes	n/a	yes	yes	n/a
7.	The hazard pictogram entitled “Biohazardous Infectious Material” set out in Schedule 3 of the <i>Hazardous Products Regulations</i> , if applicable	yes	n/a	yes	yes	n/a	yes
Retrieval information							
8.	Date, time and time zone of asystole or aortic clamping, if applicable	n/a	yes	n/a	n/a	n/a	n/a
9.	Date, time and time zone of retrieval	n/a	yes	n/a	n/a	n/a	n/a
10.	Information specific to retrieval procedure	n/a	yes	n/a	n/a	n/a	n/a
11.	Name of perfusion solution	n/a	yes	n/a	n/a	n/a	n/a
Processing information							
12.	Name of storage solution	n/a	yes	n/a	n/a	n/a	n/a

13.	Name of additives, if applicable	n/a	n/a	n/a	n/a	yes	n/a
Information for establishments							
14.	Statement that the cells have been declared safe for transplantation	n/a	n/a	n/a	n/a	yes	n/a
15.	Statement “For exceptional distribution”, if applicable	n/a	yes	n/a	yes	yes	n/a
16.	If applicable, the reasons for exceptional distribution and a statement of how the organ or cells do not meet the requirements of these regulations	n/a	yes	n/a	n/a	yes	n/a
17.	Instructions on how to report errors, accidents and adverse reactions	n/a	yes	n/a	n/a	yes	n/a
18.	Expiry date and time, if applicable	n/a	n/a	n/a	yes	yes	n/a
Establishment information							
19.	Name of retrieval establishment, its civic address and contact information	n/a	yes	yes	n/a	yes	yes

20.	Name of source establishment, its civic address and contact information	n/a	yes	yes	n/a	yes	yes
21.	Registration number of source establishment, clearly labelled as such	n/a	yes	yes	n/a	yes	yes
22.	Name of other establishment, its civic address and contact information	n/a	n/a	n/a	n/a	n/a	yes
Storage information							
23.	Statement "Human organ for transplant" or "Human cells for transplant", as applicable	n/a	n/a	yes	n/a	n/a	yes
24.	Handling instructions for storage and for storage during transportation	n/a	n/a	yes	n/a	n/a	yes

n/a: not applicable

The donor identification code must appear clearly on the product label. Product labels must include information to make it possible to trace back to the donor.

Information capable of identifying the donor

This is information that allows the cell bank or appropriate establishment to identify the donor. It includes, among other things, the donor's name, date of birth, hospital identification number and health care number.

Information specific to the retrieval procedure

The package insert must list the following:

- abnormal or noteworthy findings in the donor that are identified at the time of retrieval when the cells are distributed from a retrieval establishment to a transplant establishment or a cell bank
- for cord blood, the type of delivery, any relevant details about the delivery and the method of cord blood retrieval
- the lot numbers of any solutions used during transport of the cells

Biohazardous infectious materials

The following pictogram is to be used for biohazardous infectious materials:



Alt text: This image indicates the package contains biohazardous materials.

This pictogram must appear on the interior and exterior labels of CTO that have tested positive for infectious disease markers that would lead to the donor being excluded. Do not use the pictogram if the tests have not yet been performed or the results are not yet known.

If a generic CTO package insert is prepared, all information specific to a CTO may be printed on a label that will accompany the CTO “standard” package insert.

If no exterior packaging is used, the establishment must include the required information for the exterior label on the interior label or package insert.

CTO should either be labelled as safe for transplantation or "for exceptional distribution" but not both.

Tissues:

31. An establishment that distributes tissues must ensure that all of the applicable information, as indicated by an “X”, set out in the table to this section is provided on the interior label, in the package insert and on the exterior label.

Table to section 31: Labelling requirements for tissue

Item	Column 1 Required information	Column 2			Column 3		
		From retrieval establishment to tissue bank			From tissue bank to any other establishment		
		Interi or label	Packa ge insert	Exteri or label	Interi or label	Packa ge insert	Exteri or label
1.	Name of tissue and whether left or right side, if applicable	yes	yes	n/a	yes	yes	n/a
2.	Description of tissue	n/a	yes	n/a	yes	yes	n/a
3.	Donor identification code, clearly labelled as such	n/a	n/a	n/a	yes	yes	n/a
4.	Information capable of identifying the donor	yes	yes	n/a	n/a	n/a	n/a
5.	Donor assessment record	n/a	yes	n/a	n/a	n/a	n/a
6.	The hazard pictogram entitled “Biohazardous infectious material” set out in Schedule 3 of the <i>Hazardous Products Regulations</i> , if applicable	yes	n/a	yes	yes	n/a	yes
7.	Date, time and time zone of asystole or aortic clamping, if applicable	n/a	yes	n/a	n/a	n/a	n/a
8.	Date, time and time zone of retrieval	n/a	yes	n/a	n/a	n/a	n/a
9.	Information specific to retrieval procedure	n/a	yes	n/a	n/a	n/a	n/a
10.	Name of storage solution, if applicable	n/a	yes	n/a	n/a	yes	n/a
11.	Name of anticoagulant and other additive, if applicable	n/a	n/a	n/a	n/a	yes	n/a
12.	Statement that the tissue has been irradiated, if applicable	n/a	n/a	n/a	yes	yes	n/a
13.	Description of the disinfection and sterilization	n/a	n/a	n/a	n/a	yes	n/a

	processes that were used, if applicable						
14.	Statement "For autologous use only", if applicable	yes	yes	n/a	yes	yes	n/a
15.	Tissue-specific instructions for preparation for use, if applicable	n/a	n/a	n/a	n/a	yes	n/a
16.	Statement that the tissue has been declared safe for transplantation	n/a	n/a	n/a	n/a	yes	n/a
17.	Statement "For exceptional distribution", if applicable	n/a	n/a	n/a	yes	yes	n/a
18.	If applicable, the reasons for exceptional distribution and a statement of how the tissue does not meet the requirements of these Regulations	n/a	n/a	n/a	n/a	yes	n/a
19.	Instructions on how to report errors, accidents and adverse reactions	n/a	n/a	n/a	n/a	yes	n/a
20.	Expiry date and time, if applicable	n/a	n/a	n/a	yes	yes	n/a
21.	Name of retrieval establishment, its civic address and contact information	n/a	yes	yes	n/a	n/a	n/a
22.	Name of source establishment, its civic address and contact information	n/a	yes	yes	n/a	yes	yes
23.	Registration number of source establishment, clearly labelled as such	n/a	n/a	n/a	n/a	yes	yes
24.	Name of transplant establishment, if known, its civic address and contact information	n/a	n/a	n/a	n/a	n/a	yes

25.	Statement "Human tissue for transplant"	n/a	n/a	yes	n/a	n/a	yes
26.	Handling instructions for storage and for storage during transportation	n/a	n/a	yes	n/a	n/a	yes

n/a: not applicable

The donor identification code must appear clearly on the product label. Product labels must include information to make it easy to trace back to the donor.

Information capable of identifying the donor

This is information that allows the tissue bank to identify the donor. It includes, among other things, the donor's name, date of birth, hospital identification number and health care number.

Information specific to the retrieval procedure

The package insert must list the following:

- any abnormal or noteworthy findings in the donor that are identified at the time of retrieval when the tissue is distributed from a retrieval establishment to a tissue bank
- the lot numbers of any solutions used during transport of the tissue

Biohazardous infectious materials

The following pictogram is to be used for biohazardous infectious materials:



Alt text: This image indicates the package contains biohazardous materials.

This pictogram must appear on the interior and exterior labels of CTO that have tested positive for infectious diseases markers that would lead to the donor being excluded. Do not use the pictogram if the tests have not yet been performed or the results are not yet known.

If a generic CTO package insert is prepared, information specific to a CTO may be printed on a label that will accompany the CTO “standard” package insert.

If no exterior packaging is used, the establishment must include the required information for the exterior label on the interior label or package insert.

CTO should either be labelled as safe for transplantation or "for exceptional distribution" but not both.

When transporting tissue from a retrieval establishment to a tissue bank, establishments can add "further processing required" in addition to the labelling requirement to state "human tissue for transplant", under item #25. This or other similar statements will show that the tissue has not yet been determined safe for transplant. Avoid using statements on the label that indicate the package contains human tissue that is **not** for transplant, unless further clarification is provided on the final intended purpose of the tissue.

Organs:

32. An establishment that distributes organs must ensure that all of the applicable information, as indicated by an "X", set out in the table to this section is provided on the interior label, in the package insert and on the exterior label.

Table to section 32: Labelling requirements for organs

Item	Column 1 Required information	Column 2			Column 3		
		Deceased donor: From retrieval establishment to transplant establishment			Living donor: From retrieval establishment to transplant establishment		
		Interior label	Package insert	Exterior label	Interior label	Package insert	Exterior label
Information about donor and organ							
1.	Name of organ and whether left or right side, if applicable	yes	yes	yes	yes	yes	n/a
2.	Description of organ	n/a	yes	n/a	n/a	yes	n/a
3.	Donor identification code, clearly labelled as such	yes	yes	n/a	yes	yes	n/a
4.	All information in the donor assessment record that is not capable of	n/a	yes	n/a	n/a	n/a	n/a

	identifying the donor						
5.	ABO group and Rh factor of donor	yes	yes	n/a	yes	yes	n/a
6.	The hazard pictogram entitled “Biohazardous infectious material” set out in Schedule 3 of the <i>Hazardous Products Regulations</i> , if applicable	yes	n/a	yes	yes	n/a	yes
Retrieval information							
7.	Date, time and time zone of asystole or aortic clamping, if applicable	n/a	yes	n/a	n/a	n/a	n/a
8.	Date, time and time zone of retrieval	n/a	yes	n/a	n/a	yes	n/a
9.	Information specific to retrieval procedure	n/a	yes	n/a	n/a	yes	n/a
10.	Name of perfusion solution	n/a	yes	n/a	n/a	yes	n/a
Processing information							
11.	Name of storage solution	n/a	yes	n/a	n/a	yes	n/a
Information for transplant establishment							
12.	Statement that the organ has	n/a	yes	n/a	n/a	n/a	n/a

	been declared safe for transplantation						
13.	Statement "For exceptional distribution", if applicable	yes	yes	n/a	yes	yes	n/a
14.	If applicable, the reasons for exceptional distribution and a statement of how the organ does not meet the requirements of these regulations	n/a	yes	n/a	n/a	yes	n/a
15.	Instructions on how to report errors, accidents and adverse reactions	n/a	yes	n/a	n/a	yes	n/a
Establishment information							
16.	Name of retrieval establishment, its civic address and contact information	n/a	yes	yes	n/a	yes	yes
17.	Name of source establishment, its civic address and contact information	n/a	yes	yes	n/a	yes	yes
18.	Registration number of source establishment,	n/a	yes	yes	n/a	yes	yes

	clearly labelled as such						
19.	Name of transplant establishment, its civic address and contact information	n/a	n/a	yes	n/a	n/a	yes
Storage information							
20.	Statement "Human organ for transplant"	n/a	n/a	yes	n/a	n/a	yes
21.	Handling instructions for storage and for storage during transportation	n/a	n/a	yes	n/a	n/a	yes

n/a: not applicable

The donor identification code must appear clearly on the product label. Product labels must include information to make it possible to trace back to the donor.

All information in the donor assessment record that is not capable of identifying the donor

The donor assessment record should be redacted to remove information that could identify the donor. Do not include information that can directly identify the donor in the recipient's chart due to privacy issues. Also do not include this information on the labels that accompany the organ from the retrieval establishment to the transplant establishment.

Information specific to the retrieval procedure

List the following information on the donor's condition during retrieval of the organ (some will not apply to living donors) in the package insert when an organ is distributed from a retrieval establishment to a transplant establishment:

- hemodynamic stability (vital signs)
- blood products or fluids administered
- oxygenation levels
- relevant blood work results

- any abnormal or noteworthy findings in the donor that are identified at the time of retrieval
- the lot numbers of any perfusion solutions or solutions used during transport of the organ

Additional information may not come to light until all of the organs have been retrieved. For this reason, it's acceptable to electronically transfer (by fax or email) such information when the organ is already in transport.

Statement that the organ has been declared safe for transplantation

CTO should either be labelled as safe for transplantation or "for exceptional distribution" but not both.

As an alternative to stating on the label that the "organ has been declared safe for transplantation", we will accept wording that indicates the organ has been processed according to the CTO regulations and no contraindications to donation have been identified.

Biohazardous infectious materials

The following pictogram is used for biohazardous infectious materials:



Alt text: This image indicates the package contains biohazardous materials.

This pictogram must appear on the interior and exterior labels of CTO that have tested positive for infectious disease markers that would lead to the donor being excluded. Do not use the pictogram if tests have not yet been performed or the results are not yet known.

If a generic CTO package insert is prepared, all information specific to a CTO may be printed on a label that will accompany the CTO "standard" package insert.

Where the CTO is not packaged (for example, when organ retrieval and transplantation are done at the same time or in sequence in the same or adjacent operating room), the information that in other circumstances must appear on the interior label, package insert and exterior label must be recorded elsewhere. This could be achieved by recording the information in a document that accompanies the organ.

Additional information required:

33. A registered establishment that imports and distributes, or that only distributes, a cell or tissue must ensure that the following information is added to that required by sections 30 and 31:

(a) on the exterior label and in the package insert, the name of the establishment, its civic address and contact information

(b) on the exterior label and in the package insert, the establishment's registration number

An establishment that imports and distributes and does not take physical possession of the cells or tissues at any point (for example, the source establishment sends the cells or tissues directly to the transplant establishment) is not required to have its name and registration number on the exterior label.

An establishment that imports and distributes must provide its name and registration number to the transplant establishment so the transplant establishment can complete its records.

1.8 Quarantine (section 34)

Quarantine of cells and tissues:

34. (1) A source establishment must ensure that cells, except islet cells, and tissues are quarantined until all of the following processing activities are completed:

- a. the donor is found to be suitable after completion of the donor suitability assessment
- b. except in the case of fresh skin, bacteriological test results are reviewed and found to be acceptable, if applicable
- c. all processing records are reviewed for completeness and compliance with the standard operating procedures

Additional requirement for live donors of tissue:

(2) In addition to the requirements set out in subsection (1), the source establishment must quarantine tissues that are retrieved from live donors in accordance with section 17.2 of the tissue standard.

Quarantine refers to the following:

- the identification of cells and tissues that do not or have not yet met the screening and testing requirements of the CTO regulations and have not been declared safe for transplantation
- the preventative measures used to keep them from being distributed or used in transplantation

Cells and tissues that are implicated in any error, accident or adverse reaction investigation must also be quarantined until the investigation has determined they are safe for transplantation.

Quarantine includes:

- storing such cells or tissues in an area clearly identified for such use **or**
- preventing the release of these products for transplantation through other measures
 - for example, segregation through physical separation or through electronic identification and control systems

Quarantine does not require that these products be physically segregated if the risk of cross-contamination and improper release is managed effectively.

Exempt from this requirement are:

- fresh skin and other fresh tissue grafts until bacteriological test results are reviewed and found to be acceptable
- fresh tissue grafts as storage timeframes may not be long enough to allow for bacteriological test results to be reviewed before releasing for transplantation

In cases where HIV-1 and HCV NAT will not be performed on living tissue donors, **the tissue** must be held in quarantine for at least 180 days. At this time the donor must be retested for the following infectious disease markers before the tissue can be released (section 17.2.2 of the tissue standard):

- anti-HIV-1 and anti-HIV-2
- anti-HBc, IgG and IgM
- antibodies to hepatitis C virus (anti-HCV)
- anti-HTLV-I and anti-HTLV-II for viable, leukocyte-rich tissues

Tissue that is not considered leukocyte-rich include bone, cartilage, corneas, ligaments, sclera, skin, tendons and amniotic tissue.

If initial testing on a living donor blood specimen includes NAT for HIV-1 and HCV, the 180-day quarantine and testing a repeat blood sample is not required for any of the required infectious disease agents under 17.2.1 of the tissue standard.

1.9 Storage (sections 35 to 39)

Storage limits:

35. An establishment that distributes cells, tissues or organs and that stores cells, tissues and adjunct vessels that were not used at the time of transplantation of the organ with which they were retrieved must observe scientifically based maximum storage periods.

A maximum storage period must be determined for each CTO to maintain its integrity, function and sterility throughout its shelf life. Consider the following factors when establishing the expiration date for each CTO, as applicable:

- method of preservation, such as:
 - cryopreservation
 - lyophilization
 - dehydration
- storage conditions, such as:
 - room temperature
 - refrigeration
 - freezing
- packaging, such as:
 - ability to maintain sterility and moisture content

The maximum storage period is considered scientifically based if it meets 1 or more of the following criteria:

- the storage period for specific storage conditions has been established in standards developed by recognized professional organizations, based on established practice
- data is available in the scientific literature to support the storage period for the specific storage conditions
- the storage period for the specific storage conditions has been validated by the establishment

Establishments should provide instructions on corrective actions to be taken when temperatures rise or fall beyond the acceptable temperature limits.

Storage location:

36. An establishment that distributes cells, tissues or organs must store them in a location that has environmental conditions that maintain their safety and that is secure against the entry of unauthorized persons.

All CTOs must be stored under defined and controlled environmental conditions, which must be outlined in the SOP. Documentation that the CTOs were maintained under the appropriate environmental conditions must be kept and available upon request.

Environmental parameters for storage, such as temperature and humidity, must be controlled and should be monitored using calibrated monitoring devices. Evidence that these parameters are monitored must be kept. Temperature monitoring probes or devices should be located at points that represent extreme temperature areas, as determined by a temperature mapping study, if applicable. If the storage area has an alarm system with audible signals, alarm activation points should be set at temperatures that allow time for appropriate corrective actions to be taken before the CTO reach unacceptable temperatures. The alarm warning

should be in a location that's continually monitored or staffed so that corrective action can be taken immediately.

There must be written procedures describing the actions to be taken in the event of deviations from established storage criteria. Such an event must be appropriately investigated and documented.

Access to storage areas must be restricted to designated personnel. Where physical quarantine areas are used, they must be marked appropriately, with access restricted to designated personnel. Where electronic quarantine is used, electronic access must be restricted to designated personnel.

Storage during transportation:

37. An establishment that ships cells, tissues or organs must ensure that they are stored during transportation in appropriate environmental conditions.

This section applies to all establishments that ship CTOs.

The appropriate environmental conditions for shipping CTOs must be defined in a procedure, along with controls for such things as temperature and light. Documentation that the CTOs were maintained under the appropriate environmental conditions must be kept and available upon request.

If an establishment accepts returns of a CTO with the intent of returning the products to inventory, there must be a process in place. This process must outline the necessary documented procedures and defined acceptability criteria that will give the establishment assurance that the CTOs have been kept under appropriate storage conditions and their integrity has not been compromised. This process must be defined in the establishment's SOP and include the following documented evidence:

- the CTO was kept under appropriate conditions
- the integrity of the packaging material and the labels were not compromised
- there was no evidence of contamination or tampering
- the unopened CTO package was free of damage

An establishment cannot ship or accept any CTOs without a label.

Segregation of tissues:

38. An establishment that stores tissues must ensure that those that are intended for autologous use are segregated from those intended for allogeneic use.

Tissues for autologous use must be segregated from tissues for allogeneic use during storage to prevent the tissues from being unintentionally distributed or released. Segregation also helps to ensure that autologous tissues receive the special handling and tracking they require, as they may not have been processed under the same standards as tissues intended for allogeneic use.

Clearly label and store autologous tissues separately in restricted areas to ensure they are segregated from allogeneic tissue.

Effective segregation may be achieved by storing allogeneic and autologous tissues in different storage equipment. If they're to be stored in the same storage equipment, the storage areas for each within the storage unit must be physically separated and clearly labelled to distinguish tissues intended for autologous use from tissues for allogeneic use.

Segregation of transmissible disease agents and markers:

39. An establishment that stores cells, tissues or organs must ensure that any of them that are untested or for which the results of tests on donor blood samples are positive or reactive for transmissible disease agents or markers or are unavailable are segregated from all other cells, tissues and organs.

All CTOs must be:

- clearly labelled and stored separately in restricted areas **or**
- controlled by a system that ensures the segregation of CTOs that have been tested and deemed suitable for release or distribution from other CTOs

Other CTOs include those that are:

- untested or are quarantined until they've been tested for transmissible disease agents or markers
- unsuitable for use, unsafe, recalled and/or tested positive or reactive for transmissible disease agents or markers

The actions taken and the final status of each CTO must be recorded.

1.10 Exceptional distribution (sections 40 to 42)

Conditions:

40. A source establishment may distribute cells, tissues or organs that have not been determined safe for transplantation if all of the following conditions are met:

- a. a cell, tissue or organ that has been determined safe for transplantation is not immediately available
- b. the transplant physician or dentist, based on their clinical judgment, authorizes the exceptional distribution
- c. the transplant establishment obtains the informed consent of the recipient

Given the urgent and life-saving or -enhancing nature of transplantations, in exceptional circumstances a CTO may be needed for transplantation and a compatible CTO may be available but has yet to be deemed safe for transplantation as required by the CTO regulations.

The regulations have an "exceptional distribution" mechanism to allow CTO that may not meet all of the requirements to be distributed when there isn't a fully compliant CTO available.

These regulations are intended to maximize the safety of CTOs used in transplantation, not to determine their suitability for a specific recipient.

There are circumstances, such as using a Hepatitis C-positive CTO in a Hepatitis C-positive recipient, where a CTO may be suitable, even if this CTO has not been deemed "safe" under the regulations. Sometimes not all the information from the donor screening questionnaire is available, but the CTO is acceptable due to the direness of the intended recipient's situation. In such cases, the suitability of a CTO is a matter of clinical discretion and/or judgment.

Thus, exceptional distribution from a source establishment requires that the:

- transplant physician authorize the use of the CTO **and**
- recipient give their informed consent for that use

Recipient consent should be obtained according to applicable provincial laws and standards of practice.

Notice in source establishment's records:

41. (1) A source establishment that distributes cells, tissues or organs under section 40 must keep a copy of the notice of exceptional distribution in its records.

Notice in transplant establishment's records:

(2) The transplant establishment must keep a copy of the notice of exceptional distribution in its records.

Contents of notice:

(3) A notice of exceptional distribution must contain all of the following information:

- a. the name of the transplanted cell, tissue or organ
- b. the provisions of these regulations with which the cell, tissue or organ is not in compliance at the time of its distribution
- c. the justification for the distribution that formed the basis for the transplant physician's or dentist's decision to authorize it
- d. the name of the source establishment that distributed the cell, tissue or organ
- e. the name of the transplant establishment and of the transplant physician or dentist who authorized the distribution
- f. the time and date of the written authorization of the distribution and a copy of the authorization signed by the transplant physician or dentist

A source establishment must put a notice of exceptional distribution in their records when distributing a CTO that has met any of the exclusion criteria or transmissible disease testing requirements of the regulations. This notice must also be put in the transplant establishment records.

The notice of exceptional distribution must contain the information stipulated under subsection 41(3) of these regulations.

The notice must state the provisions of these regulations that were not met. Also, the source establishment must make sure that the information has been provided to the transplant establishment to obtain an informed consent from the recipient.

Follow-up:

42. A source establishment that distributes a cell, tissue or organ under section 40 before the donor suitability assessment is complete must, after the distribution, complete the assessment, carry out any other appropriate follow-up testing and notify the relevant transplant establishment of the results.

According to section 42, a source establishment that has not completed the donor suitability assessment and distributes a CTO under the conditions of exceptional distribution must:

- complete the assessment
- do appropriate follow-up testing after distributing the CTO **and**
- notify the relevant transplant establishment of the results

Establishments must report the following as an accident and take the actions that are prescribed in sections 44 and 51 of the CTO regulations:

- results from infectious disease testing or donor screening information were not available before exceptional distribution and transplantation **and**
- when received, the results indicate the unexpected presence of infectious disease agents in the donor

1.11 Investigation and reporting errors, accidents and adverse reactions (sections 43 to 54)

Required action:

43. (1) Subject to subsection (2), an establishment that is not a source establishment and that has reasonable grounds to believe that the safety of a cell, tissue or organ that is or was in its possession has been compromised by the occurrence of an error or accident during processing must immediately take all of the following steps:

- a. determine the donor identification codes of all implicated cells, tissues and organs
- b. identify and quarantine any other implicated cells, tissues and organs in its possession
- c. notify the following establishments:
 - i. the relevant source establishment
 - ii. if the cells, tissues or organs were imported, the establishment that imported them

Exception for importers:

(2) If the establishment that receives a notice under subsection (1) is the establishment that imported the implicated cells, tissues or organs, it only has to notify the source establishment.

Contents of notice:

(3) The notice must include all of the following information:

- a. the reasons for the establishment's belief that the safety of cells, tissues or organs has been compromised
- b. an explanation of how the safety of the implicated cells, tissues or organs may have been compromised, if known
- c. the donor identification codes of all implicated cells, tissues and organs
- d. the name of any suspected transmissible disease or disease agent, if known

Written notice:

(4) If the notice is given verbally, a confirmatory written notice must be sent as soon as possible afterwards.

The following requirements apply to establishments other than a source establishment that discovers or suspects that an error/accident has occurred during processing.

Under the CTO regulations, these establishments must immediately report to the source establishment and importer (if applicable) all known or suspected errors or accidents associated with the CTO that are or were in their possession if the errors or accidents took place during processing. They must:

- identify the CTOs involved in the error or accident **and**
- quarantine these CTOs to prevent them from being transplanted or distributed further

The source establishment and the importer are identified on the exterior label as required under section 33 of these regulations.

Upon receiving the notice under subsection 43(1), the importer must notify the source establishment. The importer should send the written notice by the next business day.

Action by source establishment:

44. (1) A source establishment that has reasonable grounds to believe that the safety of cells, tissues or organs for whose processing it is responsible has been compromised by the occurrence of an error or accident during processing must immediately take all of the following actions:

- a. quarantine any implicated cells, tissues and organs in its possession
- b. send a notice described in subsection (2) to all of the following establishments:

- i. if the cells, tissues or organs were imported, the establishment that imported them
 - ii. any source establishment from which it received the donor referral, if applicable
 - iii. any source establishment to which it made a donor referral, if applicable
 - iv. any establishment to which it distributed implicated cells, tissues or organs
- c. initiate an investigation into the suspected error or accident

Contents of notice:

(2) The notice must include all of the following information:

- a. the reasons for its belief that the safety of the cells, tissues or organs has been compromised
- b. an explanation of how the safety of the implicated cells, tissues or organs may have been compromised, if known
- c. the donor identification codes of all implicated cells, tissues and organs
- d. the name of any suspected transmissible disease or disease agent, if known
- e. a statement requiring all implicated cells, tissues and organs to be quarantined immediately and until further notice from the source establishment and specifying any other corrective action that must be taken

A source establishment must take immediate action if it **has reasonable grounds to believe**, based on its own information and the information received under section 43, that the safety of CTO that it or another establishment processed on its behalf has been compromised by an error or accident that took place during processing. The actions it is to take are listed under subsection (1).

If a source establishment believes the CTO poses any danger to potential recipients, it must notify all known establishments that received the implicated CTO by:

- phone on the same business day
- email or fax by the next business day

The source establishment must quarantine the implicated CTO according to the requirements described in section 39 and secure it from CTOs that are in compliance.

When no investigation necessary:

45. If, on receipt of a notice under subsection 43(1), the source establishment does not have reasonable grounds to believe that an investigation is necessary, it must notify the establishment to that effect in writing and provide its reasons for the decision not to conduct an investigation.

Based on notification received under section 43 and with all available information, a source establishment must include in its records a detailed rationale if it has no reason to believe the safety of the CTO for which it's responsible for processing has been compromised by an error or

accident during processing. This is set out in subsection 59 (h) of the CTO regulations. The source establishment must inform establishments that contacted it about the suspected error and accident of this decision and the actions taken for the quarantined CTO.

Action on receipt of notice:

46. An establishment that is not a source establishment and that receives a notice under section 44 or a copy of such a notice under this section must immediately take both of the following actions:

- a. quarantine all implicated cells, tissues and organs in its possession
- b. forward a copy of the notice to every establishment to which it distributed implicated cells, tissues or organs

Required action:

47. (1) Subject to subsection (2), an establishment that is not a source establishment and that has reasonable grounds to believe that an unexpected adverse reaction has occurred must immediately take all of the following steps:

- a. determine the donor identification codes of the transplanted cells, tissues or organs
- b. identify and quarantine any other cells, tissues and organs in its possession that could potentially cause an adverse reaction in the same way as the transplanted cells, tissues or organs
- c. notify the following establishments:
 - i. the relevant source establishment
 - ii. if the cells, tissues or organs were imported, the establishment that imported them

Exception for importers:

(2) If the establishment that receives a notice under subsection (1) is the establishment that imported the implicated cells, tissues or organs, it only has to notify the source establishment.

Contents of notice:

(3) The notice must include all of the following information:

- a. a description of the adverse reaction
- b. the donor identification codes of all implicated cells, tissues and organs
- c. the name of any suspected transmissible disease or disease agent, if known

Written notice:

(4) If the notice is given verbally, a confirmatory written notice must be sent as soon as possible afterwards.

Establishments other than source establishments that discover or suspect an unexpected adverse reaction has occurred must immediately report to the source establishment and the importer (if applicable) all suspected or known unexpected adverse reactions associated with a CTO. To comply with this requirement, the establishment must:

- clearly identify the CTO
- identify and quarantine other implicated CTOs (for example, from the same donor) they possess

After receiving the notice under subsection 47(1), an **importer** of a CTO must notify the source establishment of the adverse reaction.

An **unexpected** adverse reaction following the transplantation of a CTO includes:

- the **unintended** and **unforeseen** transmission of any bacterial, viral, fungal or parasitic infection (infectious disease or disease agents)
- malignancies or any other disease/disorders (for example, allergy, genetic disorder, immunological disorder) that may have originated from the donor

These must be reported to the source establishment and importer, if applicable.

Under subsection 47(3) of the CTO regulations, the notice must:

- describe the adverse reaction in detail to help with the investigation of the adverse reaction
- include the donor identification codes of the implicated CTO and, where applicable, the name of the disease or disease agent suspected to have been transmitted

The reporting of unexpected adverse reactions suspected to be associated with an CTO is time-sensitive. For this reason, the initial notice may be provided verbally. A written notice must be issued as soon as possible, preferably by the next business day.

Note: Reporting is not required when the transmission of a disease/disorder is expected (for instance, when it's known the infectious disease or disease agent was present in the donor before transplantation). An example is if a bilateral lung recipient develops *Mycoplasma hominis* pneumonia and the donor's tracheal/bronchial aspirate was known to contain *Mycoplasma hominis*. The *Mycoplasma hominis* was a known respiratory commensal in the donor, which means that the resulting pneumonia in the immunocompromised recipient was not unexpected an adverse reaction. If the donor's tracheal/bronchial aspirate was not tested or not found to contain *Mycoplasma hominis* (it's a difficult organism to culture), it would be an unexpected adverse reaction and subject to reporting and investigation.

Adverse reaction reporting applies to all CTOs, including those distributed by exceptional distribution. The requirement to report an adverse reaction for an exceptionally distributed CTO depends on whether the reason for exceptional distribution would lead someone to expect the adverse reaction. In other words, is it considered an unexpected adverse reaction.

For details on the unexpected serious adverse reactions that the source establishment must report to Health Canada, consult section 51 of the CTO regulations.

Action by source establishment:

48. (1) A source establishment that has reasonable grounds to believe that an unexpected adverse reaction has occurred that involves cells, tissues or organs for whose processing it is responsible must immediately take all of the following actions:

- a. quarantine any implicated cells, tissues and organs in its possession
- b. send a notice described in subsection (2) to all of the following establishments:
 - i. if the implicated cells, tissues or organs were imported, the establishment that imported them
 - ii. any source establishment from which it received the donor referral, if applicable
 - iii. any source establishment to which it made a donor referral
 - iv. any establishment to which it distributed implicated cells, tissues or organs
- c. initiate an investigation into the adverse reaction

Contents of notice:

(2) The notice must include all of the following information:

- a. a description of the nature of the adverse reaction
- b. an explanation of how the safety of the implicated cells, tissues or organs may have been compromised, if known
- c. the donor identification codes of all implicated cells, tissues and organs
- d. the name of any suspected transmissible disease or disease agent, if known
- e. a statement requiring all implicated cells, tissues and organs to be quarantined immediately and until further notice from the source establishment and specifying any other corrective action that must be taken

Source establishments that discover or suspect that an unexpected adverse reaction has been associated with a CTO must take action, as outlined in section 48 of the regulations. The source establishment must:

- quarantine all implicated CTOs in its control
- issue a notice to all parties listed, as described in subsection 48 (2) of the regulations
 - should include a detailed narrative of the consequences and outcomes the patient experienced when describing the unexpected adverse reaction

The source establishment must investigate the unexpected adverse reaction. At a minimum, it should include the information being requested in the notice. Refer to section 51 of the regulations for more information.

An **unexpected** adverse reaction following the transplantation of a CTO includes:

- the **unintended** and **unforeseen** transmission of any bacterial, viral, fungal or parasitic infection (infectious disease or disease agents)
- malignancies or any other disease/disorders (for example, allergy, genetic disorder, immunological disorder) that's suspected to originate from the donor

It does not include the **expected** transmission of an infectious disease or disease agent. An example is the transmission of HCV from a donor who was known to be HCV-positive before transplantation to an HCV-negative recipient. This is an expected outcome as the organ was known to be HCV-positive. It would be an unexpected adverse reaction if the recipient develops HCV following transplantation of an organ that was not known to be HCV-positive.

Under subsection 48(2) of the CTO regulations, the notice must:

- describe the adverse reaction in detail to help with the investigation of the adverse reaction
- include the donor identification codes of the implicated CTO and, where applicable, the name of the disease or disease agent suspected to have been transmitted

The reporting of adverse reactions suspected to be associated with an CTO is time-sensitive. For this reason, the initial notice may be provided verbally. A written notice must be issued as soon as possible, preferably by the next business day.

For details on the unexpected serious adverse reactions that the source establishment must report to Health Canada, consult section 51 of the CTO regulations.

Action on receipt of notice:

49. An establishment that is not a source establishment and that receives a notice under section 48 or a copy of such a notice under this section must immediately take both of the following actions:

- a. quarantine all implicated cells, tissues and organs in its possession
- b. forward a copy of the notice to every establishment to which it distributed implicated cells, tissues or organs

These requirements apply to establishments other than a source establishment that receive a notice under section 48 of the CTO regulations. Section 49 states that an establishment that is not a source establishment and that receives a notice under section 48 must quarantine all implicated CTOs over which it has control. A copy of the notice received must be sent to all establishments to which it has sent the implicated CTOs.

Requirement to cooperate:

50. An establishment must provide the source establishment that is conducting an investigation with any relevant information in its possession with respect to cells, tissues or organs that it distributed or transplanted.

All establishments contacted by a source establishment conducting an investigation must help in the investigation and provide all relevant information to the source establishment immediately. This includes, among other things:

- an inventory list of implicated CTOs with their disposition
 - number and type processed, distributed, transplanted, quarantined and destroyed
- the names of establishments to which the implicated CTOs have been distributed
- details on the adverse reaction

Requests for information made to establishments by the source establishment often reflect requests that are made to the source establishment by Health Canada.

Reports to Minister:

51. (1) A source establishment that is conducting an investigation into either of the following subject-matters must provide the Minister with the reports described in subsection (2):

- a. a suspected error or accident that is identified after distribution of cells, tissues or organs that could lead to a serious adverse reaction involving the transmission of an infectious disease or disease agent
- b. an unexpected serious adverse reaction that is thought to involve the transmission of an infectious disease or disease agent

Contents and timing:

(2) The reports must include the following information and be provided at the following times:

- a. within 24 hours after the start of the investigation, a preliminary report that includes all relevant information that is available at that time
- b. within 15 days after the start of the investigation and every 15 days after that until the final report is made, an update on any new information about the suspected error or accident or serious adverse reaction, on the progress made in the investigation during those 15 days and on the steps taken to mitigate further risks

Reporting errors, accidents and adverse reactions

For these regulations, the Minister is represented by the following Health Canada branches:

- Biological Product Compliance Program (BPCP) under the Regulatory Operations and Enforcement Branch (ROEB) for reports of an identified suspected error or accident
- Marketed Health Products Directorate (MHPD) for reports of a serious unexpected adverse reaction that may involve the transmission of an infectious disease or disease agent

Source establishments must provide all available information to Health Canada within 24 hours for:

- suspected unexpected serious adverse reactions as a result of the transmission of an infectious disease or disease agent by a transplanted CTO
- suspected errors or accidents that could lead to a serious adverse reaction as a result of the transmission of an infectious disease or disease agent

They must report errors and accidents to Health Canada by email that they identify after the affected CTO has been distributed: bpcp-pcpb@hc-sc.gc.ca.

Include the following information in this report:

- name of the suspected infectious disease and/or disease agent
- description of the CTO
- number of recipients potentially affected
- identification code of the donor (if available at the time)

This requirement to report to Health Canada does not supersede the establishment's requirement to report designated infectious diseases to public provincial/territorial health authorities.

During the course of an investigation into an adverse reaction or unexpected serious adverse reaction, the source establishment must also report to the following:

- errors or accidents that caused an adverse reaction to BPCP
- an unexpected serious adverse reaction that resulted from an error or accident to MHPD

Clarification on accident reporting

The following are circumstances under which certain test results that are received post-transplant must be reported to Health Canada as an accident:

- Blood cultures that indicate an active/acute infection of clinical significance, such as sepsis, which is a clear contraindication to donation:
 - A source establishment would only be able to distribute organs from a septic donor under the exceptional distribution provisions if the results were available before distribution.
 - A positive blood culture result received post-transplant that indicated sepsis is an unexpected result and thus meets the definition of an accident.
 - Alternatively, some localized infections identified by positive urine and sputum cultures might be considered "expected". In this case, the source establishment is not required to report positive results received post-transplant as accidents.
- Positive donor toxoplasmosis test results in heart donors:
 - A source establishment is not required to report these results, whether or not they are received pre- or post-transplant.
 - Positive test results are not considered unexpected due to the prevalence of toxoplasmosis in the general population. Thus, results that are received post-

transplant do not constitute an accident under the CTO regulations and do not need to be reported.

- This also applies to positive CMV and EBV donor test results.

The source establishment must forward all test results to:

- the transplant programs **and**
- other source establishments that processed other cells and tissues from the same donor

In another example, bacteria or fungi found in the blood of a donor could be clinically significant to the health of the recipient and should be reported as an accident to Health Canada. The source establishment should report all unexpected positive blood cultures (received post-transplant) if it doesn't have a protocol in place to determine clinical significance. This reporting could be reduced if the establishment has a protocol that:

- is developed in consultation with experts in microbiology and transplant transmissible diseases
- differentiate between:
 - a. positive blood cultures that indicate bacteremia or fungemia versus those that likely resulted from the blood specimen becoming contaminated while handled
 - b. bacteremia or fungemia that are clinically significant versus those that are not

The source establishment must report to Health Canada as follows:

- if it implemented the protocol described in a), must report unexpected positive blood cultures that indicate bacteremia or fungemia
- if it implemented protocols described in a) and b), must report unexpected positive blood cultures that indicate bacteremia or fungemia and are considered clinically significant

Regardless, the source establishment should immediately report all positive blood culture results, received post-transplantation, to the transplant establishment. The transplant establishment will then be able to assess the clinical significance to the organ recipient and provide timely medical treatment, if necessary.

Tissue transplant establishments that perform microbial testing before transplantation must inform source establishments if the culture results indicate an active/acute infection of clinical significance. This is outlined in section 43 of the CTO regulations.

Not all situations must be reported:

- Example: For ocular tissues, if the eye bank received a report that a positive bacteria result was found by another source establishment for a particular donor but the bacteria are acceptable (for instance, not an active infection of clinical significance for ocular tissue)

Error and accident reporting (directed to BPCP)

Email your reports to BPCP: bpcp-pcpb@hc-sc.gc.ca.

Use the following error and accident report form to report:

- [Human cells, tissues and organs for transplantation: Error or accident preliminary investigation report form \(FRM-0172\)](#)

Investigation

During an investigation, a source establishment must determine:

- if any other CTOs are affected
- the status of the implicated CTO
 - number of CTOs processed, distributed, quarantined, transplanted and destroyed **and**
 - number of establishments contacted

Source establishments must:

- consider if additional tests are required, such as donor testing, archived serum sample testing or bacteriological testing
 - testing results must meet the requirements of the CTO regulations
- develop a protocol to describe the interpretation of laboratory results
- develop criteria for acting on positive (reactive) results

Any documentation on the investigation must be available for Health Canada to review when we request it.

Reports

Every 15 calendar days after an investigation begins and until the final report is submitted, the source establishment must update BPCP on the following:

- new information about the suspected error or accident
- progress made in the investigation during those 15 days **and**
- steps taken to mitigate further risks, including root cause analysis and planned corrective actions

The updates must include information on the number of:

- CTOs processed, distributed, quarantined, transplanted and destroyed **and**
- establishments contacted

The Minister may ask an establishment to recall a product based on this information. A recall is a set of actions that an establishment takes to remove a product from the market if the product:

- poses a health risk to humans **or**
- contravenes the *Food and Drugs Act*

At any time during the investigation, Health Canada can ask for more information, as set out in section 14 of the CTO regulations.

A source establishment does not need to report an error or accident to the Minister if it can determine before an investigation starts that no CTOs exported to Canada were affected. However, the establishment should inform the Minister of any errors, accidents or adverse reactions involving a CTO not exported to Canada, to avoid miscommunications.

If it's determined during the course of the investigation that a CTO involved in the error or accident was exported to Canada, the establishment must provide to the Minister all reports described in sections 51 and 54 of the CTO regulations.

Reporting unexpected serious adverse reactions

Source establishments that suspect an unexpected serious adverse reaction involving the transmission of an infectious disease or disease agent from a donor to a recipient by transplanted CTO has occurred must:

- report to Health Canada with all available information on the unexpected serious adverse reaction **and**
- do so within 24 hours of starting the investigation

We encourage source establishments to voluntarily report other unexpected serious adverse reactions that are thought to originate from the donor of the transplanted CTO. These include the transmission of:

- malignancies
- other disease/disorders, such as:
 - allergy
 - genetic disorder
 - immunological disorder

Information on preliminary (initial), follow-up and final reports

Use the following form for your preliminary (initial) report and any follow-up reports to MHPD:

- [Mandatory adverse reaction form for industry](#)

Preliminary (initial) report

The source establishment must provide MHPD with the following within 24 hours of an investigation into an unexpected serious adverse reaction:

- risk mitigation measures you took
- other relevant information that is available at the time

This requirement is outlined in to section 51(2)(a) of the CTO regulations.

This information should include the:

- identification code of the donor(s) (if known)
- date the CTO was retrieved from the donor
- transplantation date
- date and description of the adverse reaction
- suspected infectious disease and/or disease agent
- implicated CTO
- distribution of CTO from the implicated donor

We require 1 reporting form for each affected recipient. Each affected recipient should have a unique source establishment report number.

15-day update (follow-up) reports

The source establishment must provide MHPD an update on the status of the investigation and any further risk mitigation measures taken:

- within 15 days after the start of the investigation
- every 15 days after that until the final report is submitted

This is outlined in section 51(2)(b) of the CTO regulations.

This update should also include:

- relevant clinical information, such as:
 - progress/outcome of the patient and other implicated recipients
 - results of laboratory investigations
- information on the root cause of the infection, such as:
 - evidence of a causal association to the donor
 - how donor transmission was excluded
 - actions taken

Clearly mark all updated information on the reporting form and present the steps taken as part of the investigation in chronological order. You may attach additional pages to the Mandatory Adverse Reaction Reporting Form for Industry if you need more space.

MHPD may ask for more information after receiving the adverse reaction report. The type of information requested is outlined in section 14 of the CTO regulations. If an establishment other than the source establishment has this information, it must cooperate with the source establishment. This is outlined in section 50 of the regulations.

Contact us

Source establishments should send adverse reaction reports covered by this guidance document by fax to:

Canada Vigilance Program
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Tunney's Pasture
Address Locator: 1908C
Ottawa ON K1A 0K9
Fax: 613-957-0335
Email for enquiries: canada.vigilance.cto@hc-sc.gc.ca

When investigation shows no contamination or compromise:

52. (1) If the results of the investigation show that the implicated cells, tissues or organs are not contaminated or compromised, the source establishment must notify every establishment that was notified under section 44 or 48 to that effect in writing and that they may be released from quarantine.

Forwarding of copies of notice:

(2) On receipt of a notice under subsection (1), an establishment that is not a source establishment must forward a copy of the notice to every establishment to whom it distributed implicated cells, tissues or organs.

Implicated CTOs that are determined to be not contaminated may be distributed. The source establishment:

- should prepare a list of the identification codes for all CTOs that are not contaminated
- must notify, in writing, all the establishments that were previously notified under section 44 or 48 of the CTO regulations that they may distribute the CTOs with the identification codes specified in the list
- may distribute the CTOs it has that have the identification codes specified in the list

When investigation inconclusive or shows contamination or compromise:

53. (1) If the results of the investigation show that some or all of the implicated cells, tissues or organs are contaminated or compromised, or the results are inconclusive, the source establishment must notify every establishment that was notified under section 44 or 48 to that effect in writing and that they may not be released for distribution.

Forwarding of copies of notice:

(2) On receipt of a notice under subsection (1), an establishment that is not a source establishment must forward a copy of the notice to every establishment to whom it distributed implicated cells, tissues or organs.

Implicated CTOs that are determined to be contaminated or where the results are inconclusive must be destroyed or reserved for distribution under exceptional distribution. This is outlined in section 40 of the CTO regulations.

The source establishment must:

- prepare a list of the identification codes for CTOs that are contaminated or where the results of the investigation are inconclusive
- notify, in writing, all the establishments that were previously notified under section 44 or 48 that they must quarantine all implicated CTOs with the identification codes specified in the list as these are not safe for transplantation
- destroy the implicated CTOs that it has in its possession, unless they're reserved for distribution under exceptional distribution

All establishments that receive a notification must follow the directions on handling the implicated CTOs.

Final report to Minister:

54. (1) On completion of an investigation, the source establishment must submit a detailed final report to the Minister that contains at least all of the following information:

- a. the results of the investigation
- b. the final disposition of the cells, tissues and organs that were the subject of the investigation and the reasons for that disposition
- c. any corrective actions taken

Summaries of final reports:

(2) The source establishment must send a summary of the final report to every establishment that was notified under section 44 or 48.

Forwarding of summaries:

(3) An establishment that receives a summary under subsection (2) must send a copy of it to every establishment to which it distributed implicated cells, tissues or organs.

Once the source establishment has finished its investigation, it must notify and provide a final report to BPCP or MHPD, whichever is appropriate. The final report must contain enough details and indicate the results of the investigation. It

should also:

- include conclusions
- specify infectious agent(s)
- provide test results and follow-up and corrective actions taken **and**
- give details of the final disposition of the CTO:
 - number processed, distributed, transplanted, quarantined, destroyed

Other requirements

The source establishment must investigate and document all errors and accidents and adverse reactions regardless of the reporting obligation to Health Canada.

Under subsection 59(h), a source establishment must keep the following records:

- any errors, accidents and adverse reactions associated with CTOs it has processed or transplanted, and corrective actions taken
- its investigation along with its assessment and monitoring

Under subsection 60(f), a transplant establishment must keep records of any errors, accidents and adverse reactions associated with CTOs it has transplanted, and any corrective action taken.

Furthermore, establishments are required under subsection 74(2) to review any SOP based on the receipt, from the source establishment, of a summary report of an error, accident investigation or a follow up report to an adverse reaction investigation that revealed a deficiency.

1.12 Records (sections 55 to 63)

Record quality:

55. Records kept by an establishment must be accurate, complete, legible and indelible. Except for distribution records, all records must identify the person who is doing the activities and the dates of the various entries.

Establishments must have a system in place to ensure the accuracy of their records, including transcribing test results manually. Transcribed data must be independently verified.

Records must be understood and made accessible. Use indelible ink for handwritten records and cross out text that's corrected in a paper document. Also, initial or sign any correction, entry or notation made after the record was completed. Date these so the reader can distinguish which information is original and which is changed.

Use a standardized format for dates (for example, YYYY/MM/DD or MM/DD/YY) for all records.

Records must be preserved to ensure they remain complete and accurate over time and accessible when needed. Establishments may use microfiche, microfilm or other ways to keep permanent records. A person other than the person who transferred the information must verify what media has been used to hold this information.

Guiding principles for transferring to secondary medium and destroying original records

Transfer

The source establishment **should** validate and document the transfer process in appropriate procedures, and ensure that:

- measures are in place to verify that appropriately trained people have transferred the information accurately

- for example, someone not involved in the transfer attesting or certifying copies
- corrections to the original data can be clearly captured in the secondary medium
- The process follows existing standards when possible
 - for example, Canadian General Standard Board

For records that are copied off-site, a contract signed by the establishment and the service provider must describe the requirements in detail, for example:

- transporting to the site
- ensuring copy quality
- outlining the storage conditions
- destroying original documents, where relevant

Electronic or other system

We recommend that you validate the format and system where documents are retained for their intended use. Include the following:

- design to ensure any alterations and updates, if permitted, such as source, date and content (for instance, audit trail) can be traced
- back-ups at regular intervals
- security measures in place and documented to protect against data corruption from accidental deletion, equipment failures, material deterioration or other hardware and software problems
- controlled access to appropriate individuals (by using passwords, for example)
- plan for future accessibility when technology, personnel or third-party contractors change over time
- location of records that permits immediate access

Destroying original records

It may be acceptable to destroy original paper records after they have been transferred to a secondary medium if the principles discussed in this document are in place. You should document the process used to destroy the original paper records in appropriate procedures. Additional requirements that may apply to the destruction of personal/confidential information should also be considered.

Other considerations

Other requirements may apply to the transfer, storage and destruction of records, including:

- provincial
 - for example, medical records
- institutional
- legal
 - for example, transfer to an electronic format may not be acceptable when it contains a watermark or official seal

Donor identification code for source establishment

56. (1) A source establishment must assign a donor identification code to each donor of a cell, tissue or organ for which it has responsibility.

Donor identification code for all establishments

(2) Every registered establishment and transplant establishment must ensure that the donor identification code is a component of its records system.

The source establishment assigns the donor identification code. This is a unique identifier. It corresponds to all CTOs from that donor processed by or on behalf of the given source establishment. The donor identification code will associate the CTOs with information about the donor from which it was retrieved.

Depending on how many CTOs were retrieved, a donor may have more than 1 donor identification code associated with them. This is because the source establishment may be different for various types of CTOs retrieved from the donor.

All source establishments must assign a donor identification code to every donor it is responsible for processing.

For example, in the case of a multiple tissue/organ donor, where bone, ocular tissue, kidney and liver were to be retrieved from the donor, an organ donation organization (ODO) would be the source establishment responsible for the processing and safety of the organs. The source establishment would assign a donor identification code to the organs.

Similarly, the tissues might be sent to a comprehensive tissue bank for processing. This tissue bank would assign a donor identification code to the tissues that it processes from that donor. Thus, the donor would be associated with 2 different donor identification codes. If, however, the bone and ocular tissues were sent to a bone and an eye bank rather than a comprehensive tissue bank, each of these establishments and the ODO would assign a donor identification code. The donor would then be associated with 3 different identification codes.

We recognize that 1 identification code per donor may be preferable. However, there are generally different source establishments for each of the different types of CTO, located in different provinces, regions and countries. The logistics of having 1 identification code for each donor would be very difficult. It would require all of the individual programs to collaborate to create a single donor coding system or the establishment of a single national organ and tissue donation body.

Although it's not possible to have a single identification code for every CTO donor at this time, it's still necessary that each CTO be associated with information about the donor from which it was retrieved and any processing activities that it underwent. For this reason, subsection 56(2) of the CTO regulations requires that the donor identification code be a component of the record-keeping system used by all registered and transplant establishments.

A source establishment may assign other numbers or codes to a CTO in addition to the donor identification code to help with their own record-keeping. However, all identifiers must be

traceable to the original donor. Likewise, other establishments involved in processing a CTO may also assign their own numbers or codes to that CTO for their records.

Under sections 30 to 32 of the CTO regulations, the donor identification code must be clearly labelled as such. This will ensure that everyone who handles a CTO will be able to identify and record the donor identification code that was assigned by the source establishment.

Requirement

57. An establishment's records must contain information with respect to all cells, tissues and organs that it processes, distributes, imports or transplants that identifies:

- a. the establishment from which it receives the cells, tissues and organs
- b. all establishments to which it distributes the cells, tissues and organs

Records must contain information about the establishment from which CTOs are received and establishments to which CTOs are distributed. Requiring each establishment to record this information makes it possible to trace the CTOs throughout the chain of distribution.

In addition to the name of each establishment, records should include the:

- identity of each CTO received or distributed, by the donor identification code and other attributes with the corresponding date
- information from the retrieval establishment that identifies the donor
- establishment address
- establishment phone and fax numbers
- contact information in case of an emergency
- emergency phone number
- establishment registration number, if applicable

Shipping documents

58. An establishment's records must include all shipping documents with respect to cells, tissues and organs that it ships to another establishment.

Source establishment records

59. The source establishment must keep records with respect to cells, tissues and organs that it processes that contain at least all of the following information:

- a. the donor identification code
- b. documentation showing completion of the donor suitability assessment
- c. a description of the cells, tissues and organs retrieved from the donor
- d. if applicable, the name of any source establishment from which it received a donor referral or to which it made a donor referral
- e. the name of the retrieval establishment
- f. documentation of all processing activities
- g. the notice of exceptional distribution, if any

- h. documentation of any reported errors, accidents and adverse reactions and their investigation, if any, in connection with cells, tissues or organs retrieved from the donor that it banked or distributed and any corrective action taken

Information on traceability does not need to be in the donor chart. But it must be in the source establishment's records.

Records are a critical component of any quality assurance (QA) system. They are documented evidence of compliance. Source establishments must keep these records along with the performance of each significant step when processing, importing, storing, distributing (including exceptional distribution), transplanting and investigating errors, accidents and adverse reactions for each CTO. All steps must be clearly associated with the person, time/date and location of such activities.

Aside from other recording requirements that are covered under various sections of this document, the following requirements are specific to processing activities.

Processing equipment records

Source establishments must keep records for each piece of equipment that could affect the quality and the safety of the CTO. These records must include, at the least, the:

- identity of the equipment
- serial number or other unique identifier
- manufacturer's name and contact information
- date the equipment was received, put into service and, if applicable, out of service
- manufacturer's instructions, if available, or reference to their retention
- equipment performance records that confirm the equipment's suitability for use (equipment qualification), including calibration and/or verification records
 - should include dates of tests, test results, adjustments made, acceptance criteria and frequency of checks
- schedules of completed and anticipated maintenance activities
- any damage, malfunction, modification or repair of the equipment
- usage log sheet **and**
- records of recall

The records should be readily available for the lifespan of the equipment. Each item of equipment should be uniquely labelled, marked or otherwise identified.

Testing records

Source establishments must have records for all laboratory tests of transmissible disease markers. The tests must be done in accordance with the corresponding test kit manufacturer's instructions.

Where applicable, records of written agreement between the source establishment and any testing laboratory should be in place to provide relevant information. There should be records showing agreements for the following:

- appropriate tests performed on each sample
- the laboratory followed the manufacturer's instructions and performed the tests within the limits and timeframes suggested by the manufacturer
- the test kits used to test donors for the transmissible disease agents comply with these regulations
- a current test kit list and notification when changes are made to the test kit
- testing validation data
- method for reporting results to source establishment
- interpretation of test results

Testing laboratories should make available to the source establishment its detailed testing records, logs and other supporting documents. These documents should include the:

- name of the test kit
- lot number
- name, lot number and expiry date of the solutions and reagents used
- expiry date
- name of the manufacturer
- testing validation data
- records of recall, if applicable

Critical supplies records (such as devices, instruments, reagents, containers)

Records must be kept for each critical supply item that is used during processing and that could affect the quality and the safety of the product. These records must include:

- identity of the supply, including type, lot number
- manufacturer's name
- expiration date, if applicable
 - get clarification from the manufacturer if the date is not clear
- manufacturer's instructions, if available
- records showing that non-disposable instruments used in processing are cleaned, disinfected and/or sterilized to prevent contamination and cross-contamination according to written procedures

Where applicable, records of written agreement that show relevant information such as roles and responsibilities between the source establishment and the retrieval establishment must be kept. The written agreement should also attest that the records are in compliance with the CTO regulations.

If an error, accident or adverse reaction occurs, a report must be written that describes the incident, the investigation, corrective actions taken and any follow-up activities required.

In addition to the donor identification code, other attributes such as a description of the CTO must be unique to avoid identity mix-up (for example, Achilles Tendon L and Achilles Tendon R).

In cases of exceptional distribution, source establishments must keep in their records:

- documentation of a notice of exceptional distribution as described in subsection 41(3) of the CTO regulations
- follow-up assessment and testing results of the donor

Transplant establishment records

60. The transplant establishment must keep records with respect to cells, tissues and organs that it transplants that contain at least all of the following information:

- a. a description of the transplanted cells, tissues or organs
- b. the donor identification code
- c. the registration number of the source establishment
- d. the notice of exceptional distribution, if any, and confirmation that the donor suitability assessment was completed as required by section 42
- e. information that allows the identification of the recipient
- f. documentation of any errors, accidents and adverse reactions and their investigation in connection with those cells, tissues or organs and any corrective action taken

The recipient's chart does not have to keep information on traceability. This information must be in the transplant establishment's records, however.

In addition to the donor identification code, other attributes such as a description of the CTO must be unique to avoid identity mix-up (for example, Achilles Tendon L and Achilles Tendon R).

For exceptional distribution, the transplant establishment's records must contain the following:

- a copy of the notice of exceptional distribution
- documentation of follow-up assessment and testing

Establishments to cooperate

61. An establishment must provide the source establishment and the transplant establishment with all of the information described in sections 59 and 60, respectively, that it possesses to complete the establishment's records.

When 2 or more establishments are involved in CTO-related activities, each establishment must:

- delineate the relationship and responsibilities of each, in writing
- keep documentation

Establishments that are contacted by a source establishment or a transplant establishment for any information described in sections 59 and 60 of the CTO regulations must provide that establishment with all the information requested.

Retention: 10 years after transplantation

62. (1) An establishment must keep the following records for at least 10 years after the date of transplantation, if known, or for at least 10 years after the date of distribution, final disposition or expiry of the cell, tissue or organ, as the case may be, whichever is the latest:

- a. the records described in section 57
- b. the records described in section 59, except paragraph (h)
- c. the records described in section 60, except paragraph (f)
- d. the record of destruction or other disposition of the cell, tissue or organ, if applicable

Retention: 10 years after record creation

(2) An establishment must keep the following records for 10 years after the date of their creation:

- a. the records described in paragraphs 59(h) and 60(f)
- b. reports of audits conducted under section 76, if applicable

Retention: employee records

(3) An establishment that distributes cells, tissues or organs must keep records of the qualifications, training and competency of its employees for 10 years after the time an individual ceases to be an employee of the establishment.

Retention: standard operating procedures

(4) An establishment that distributes cells, tissues or organs must keep a copy of every version of its standard operating procedures for 10 years after they are superseded by a new version.

With the exception of subsections 59(h) and 60(f), processing activity records, as well as records of importation, distribution and transplantation of the CTO that the establishment has in its possession must be kept as follows:

- establishment knows the date of transplantation: at least 10 years after the date of transplantation
- establishment doesn't know the date of transplantation: at least 10 years after the expiry date, final disposition date or final distribution date, whichever is the latest

Under subsections 59(h) and 60(f), records must be kept for 10 years from when they are created. Other records described in section 62 of the CTO regulations are to be kept for 10 years from when the employee left the establishment [subsection 62(3)] or the date that a new version of the SOP came into effect [subsection 62 (4)].

Storage of records

63. An establishment that distributes cells, tissues or organs must store records in a location that has appropriate environmental conditions and that is secure against the entry of unauthorized persons.

Storage areas for records must maintain the integrity of the records and access must be restricted to designated personnel.

For records stored off-site, an SOP must outline specific requirements, such as for:

- transport to the site
- copy quality
- storage conditions
- document retrieval
- destruction of original documents, if relevant

1.13 Personnel, facilities, equipment and supplies (sections 64 to 69)

Sufficient number and qualifications:

64. (1) An establishment that distributes cells, tissues or organs must have sufficient personnel who are qualified by education, training or experience to perform their respective tasks to carry out the establishment's activities.

Competency:

(2) An establishment that distributes cells, tissues or organs must have a system for the orientation and training, both initial and ongoing, of personnel and for the evaluation of their competency.

Not enough or underqualified staff increases the risk of errors and accidents. There must be a sufficient number of qualified personnel to perform the tasks required.

An establishment should prepare and keep a current organizational chart that shows lines of responsibility. Job descriptions must describe the qualifications and functions of each staff position.

Personnel must receive initial and ongoing training appropriate for their duties.

Training programs must be available and must include an assessment of competency that may include the following:

- direct observation of performance
- monitoring of recording and reporting
- written tests to assess problem-solving skills
- assessment of knowledge of operating procedures and theory **and**
- assessment of how personnel who conduct routine testing perform in proficiency tests

Personnel affected by a new or revised SOP must receive training before performing any tasks associated with a new or revised SOP. Training records must confirm when training took place, include information verifying this, such as the employee's signature, and indicate if technical or competency testing is required.

The medical director or scientific director may delegate responsibilities to qualified persons within the establishment, in accordance with the SOP.

Establishments that distribute must keep records of the qualifications, training and continuing competency of individuals.

Requirements

65. The facilities of an establishment that distributes cells, tissues or organs must be constructed and maintained to permit all of the following:

- a. the carrying out of all of its activities
- b. the efficient cleaning, maintenance and disinfection of the facilities in a way that prevents contamination and cross-contamination
- c. environmental and microbiological monitoring and control appropriate to the areas where its activities are carried out
- d. controlled access to all areas where its activities are carried out

Premises must be:

- located, designed, constructed and adapted to suit the activities that are carried out
- designed and furnished to reduce the risk of errors and accidents and microbiological contamination
 - design should ensure that operations can proceed in an orderly manner
- designed to allow for effective decontamination and to prevent cross-contamination when personnel and materials are going between different areas

The sanitation program should include:

- cleaning requirements applicable to all areas, with emphasis on processing areas that require special attention
- the list of products for cleaning and disinfection, along with the manufacturer's instructions
- the responsibilities of outside contractors
- disposal procedures for waste material and debris
- pest control measures

Access to areas where aseptic activities are conducted and where products and samples are stored must be controlled.

Establishments should have microbial and environmental monitoring procedures, with alert and action levels set for areas where aseptic activities are conducted and susceptible products are processed or packaged.

There must be no direct access from the areas where processing is carried out to the exterior of the building, except in emergencies.

Requirements for equipment

66. An establishment that distributes cells, tissues or organs, in carrying out its processing and storage activities, must use equipment that is cleaned and maintained and, whenever applicable:

- a. qualified for its intended purpose
- b. calibrated
- c. disinfected or sterilized before each use
- d. requalified or recalibrated, as appropriate, after any repair or change is made to it that results in a change to its specifications

Establishments must ensure that all equipment can be easily cleaned and maintained. Cleaning schedules must be established and followed to prevent contamination, cross-contamination or spread of infectious diseases. The cleaning procedure must be validated to ensure that contaminants and cleaning product residues that could interact with the CTOs are removed.

Equipment must be:

- disinfected or sterilized using validated methods to reduce the risk of contamination and cross-contamination, where possible
- qualified and/or calibrated according to the manufacturer's instructions to ensure they consistently operate within established tolerance limits, where applicable
 - maintenance, recalibration and requalification must be performed according to the manufacturer's instructions

For more information on equipment, refer to section 5.3 of the general standard.

Requirements for storage equipment

67. An establishment that distributes cells, tissues or organs that uses equipment to store cells, tissues or adjunct vessels that are not used immediately in organ transplantation must ensure that the equipment maintains appropriate environmental conditions.

Establishments must:

- store all CTOs according to conditions described on the label (for example, controls for temperature, humidity, light)
- document that the CTOs were kept under the appropriate environmental conditions

Environmental parameters for storage, such as temperature and humidity, must be controlled and should be monitored using calibrated monitoring devices.

Establishments must:

- record temperatures and/or liquid nitrogen levels at defined intervals
- keep records documenting that these parameters are being monitored

Establishments should:

- locate temperature monitoring probes or devices at points that represent extreme temperature areas, as determined by a temperature mapping study
- set alarms to activate at temperatures that allow time for appropriate corrective actions to be taken before the CTOs reach unacceptable temperatures (if storage area has an alarm system)
 - alarm should signal in a location that's continually monitored or staffed so that corrective action can be taken immediately

Procedures describing the actions to be taken in the event of deviations from established criteria must be written. Such events must be appropriately documented and investigated.

Processing supplies

68. An establishment that processes cells, tissues or organs must use qualified supplies for those activities that could affect the safety of the cells, tissues or organs, and must store solutions, reagents and other supplies under appropriate environmental conditions.

The person responsible for the establishment's QA (medical director, the scientific director or designate) must establish acceptance criteria for the supplies used to process CTOs.

Supplies should be quarantined until the person in charge of QA finds each specific lot is acceptable for use. The conditions of use and storage of each supply must be appropriate as instructed by the manufacturer. The expiry dates of supplies and ongoing storage conditions must be strictly observed.

Cleaning supplies

69. An establishment that processes cells, tissues or organs must ensure that it uses supplies for cleaning, maintenance, disinfection or sterilization that do not react with, or that are not absorbable by, the cells, tissues or organs.

The choice of cleaning supplies used in the processing areas should be reviewed to ensure that they do not negatively impact the quality and safety of the CTOs they come in contact with. The cleaning supplies must be of the appropriate grade and quality.

Cleaning supplies that could affect the safety of the CTOs must:

- be used or stored according to the manufacturer's instructions or as stated on the label
- not generate toxic vapours or degradation products that could contaminate the CTOs

The name and the lot numbers of supplies that are used to clean, disinfect or sterilize equipment and instruments should be recorded and the expiry dates must be strictly observed.

1.14 Quality assurance system (sections 70 to 76)

Application:

70. Sections 71 to 76 apply only to establishments that distribute cells, tissues or organs.

Under these regulations, all registered importers and establishments that distribute as intermediaries and source establishments must have a QA system (refer to the following section 71 for details). This includes source establishments that are also transplant establishments for lymphohematopoietic cells that are not banked and organs from living donors.

Quality assurance system required:

71. An establishment must ensure that it has a quality assurance system in place that complies with the requirements of these Regulations for all activities that it carries out.

A QA system must be established to ensure the maximum quality and safety of the CTOs distributed by the establishment. Quality assurance consists of all the organized arrangements made and the measures taken to reach this objective.

The QA system **must** have the following elements.

Management requirements (sections 71 to 76):

- QA system that is defined, documented, implemented, maintained and kept up to date
- an organizational structure that defines and documents personnel responsible for any activities under these regulations
- policies, processes and procedures that cover all activities (sections 72 to 75)
- senior management responsible for attaining quality objective
- QA policies, processes, programs, procedures and instructions documented and communicated to all relevant personnel
 - management to ensure that documents are understood by personnel and are implemented
- satellite facilities are operated in accordance with the establishment's QA system

Documentation system (sections 72 to 75):

- define, document and maintain procedures to control all documents and information that are part of quality documentation system
- have a system to ensure that all documents required under the CTO regulations are kept and stored in accordance with sections 62 and 63
- uniquely identify documents relevant to the QA system and ensure they're clear, concise, in a consistent format and meet establishment policies

- ensure only the current version of all documents (SOPs and policies) are available for use and expired versions out of circulation

Other systems:

- system for employing qualified personnel and providing ongoing personnel training (section 64)
- system or program for the security and maintenance of the establishment's facilities (section 65)
- equipment (section 66)

Computer systems/data processing control used to process and distribute CTOs and other regulated activities:

- processes for authorizing and documenting modifications to the computer system
- policies that define who may use the computer, access recipient/donor data and authorized to enter and change results or data or modify computer programs
 - should have processes and procedures to support the maintenance and security of computer systems

Process control:

- carry out processes under controlled conditions, according to written procedures prepared by qualified personnel (sections 72 to 75)
- reflect and approve changes to processes, materials, equipment and facilities that may impact the quality and safety of CTOs in the written procedures before they're implemented.
- approve changes to SOPs corresponding to section 72 (subsection 73(d))

Quality control:

- processes and procedures to monitor and control the quality and safety of the CTO, as applicable

Suppliers for critical supplies and services (section 68):

- policies, processes and procedures (such as agreements and audits) to assess that suppliers of critical materials and services can consistently meet specified requirements

Reporting and investigating errors, accidents and adverse reactions (sections 43 to 54):

- management system to ensure that errors, accidents and adverse reactions are identified, recorded, reported, evaluated, investigated and followed
- approve and implement corrective action when required
- have a control system that permits a complete and rapid recall of any CTO that has been distributed, when required

Audit program (section 76)

The QA system **should** have the following elements.

Preventive action:

- procedures for preventive action that should include data analysis (such as trend- and risk-analyses and monitoring effectiveness)
- action plans developed, implemented and monitored to reduce non-conformance and maximize opportunities for improvement, if preventative action is required

Customer complaints and corrective actions:

- policy and procedures for investigating and handling complaints

Standard operating procedures required

72. An establishment must have standard operating procedures with respect to the safety of cells, tissues and organs for all activities that it carries out.

An establishment must also:

- describe activities that could affect the safety and quality of CTOs in written SOPs that have been approved by the medical director, scientific director or designates
- ensure the SOPs are part of the establishment records for processing, distributing and importing CTOs

For example, such SOPs could be in place for:

- processing
- label control and verification
- final safety assessment of CTOs
- storage, distribution, importation and record-keeping
- reporting, notification of and investigating adverse reactions, errors and accidents
- issuing recalls
- facility cleaning and maintenance and environmental monitoring
- maintenance, cleaning, calibration and qualification of equipment and instruments, if applicable
- exceptional distribution
- personnel training

SOPs contains instructions or directions so that personnel can perform activities and document consistently and ensure they're in compliance with regulatory requirements.

Requirements

73. The standard operating procedures must meet all of the following requirements:

- a. be in a standardized format
- b. be approved by the medical director or scientific director
- c. be available for use at all locations where the relevant activities are carried out
- d. have any changes to the procedures approved by the medical director or scientific director before being implemented
- e. be kept up-to-date

For the format of each SOP, indicate, at a minimum:

- type of procedure
- title and purpose of procedure
- unique number identifying the document
- date the SOP took effect and date(s) of revisions
- signature of the authorizing person (medical director, scientific director or designate) and date of authorization
- page numbers
- outline of steps and instructions to be followed in described procedure which matches the details in the processing records (for example, worksheets, forms or computer screens), if applicable
- staff categories responsible for performing all or part of the steps in the SOP
- references to publications cited in support of policies and procedures

SOPs (and changes to these) must be kept in a document control system that ensures they are current and authorized by the medical director, scientific director or designates. In an urgent situation, a change to a current operating procedure is allowed if the medical director or scientific director approve, sign, date and document the reason for the change. Invalid or obsolete documents must be promptly removed so they're not used in error.

Routine review

74. (1) An establishment must review its standard operating procedures every two years and again after any amendment to these regulations.

Supplementary review:

(2) An establishment that receives a summary of a final report of an error, accident or adverse reaction investigation or the report of an audit either of which reveals a deficiency in a standard operating procedure must review that procedure.

SOPs must be reviewed and/or revised every 2 years at a predetermined period, by a knowledgeable person(s). The review must be documented. SOPs must also be amended to reflect changes to the CTO regulations. The medical director, scientific director or their designates must approve and document the changes, including the reason for the changes.

Keep all SOPs for 10 years after they have been superseded by a new version (subsection 62(4) of the CTO regulations).

Records of compliance

75. An establishment must keep records that demonstrate that it has implemented its standard operating procedures.

Records must indicate the dates when SOPs and their revised versions are implemented.

Audits

76. An establishment must conduct an audit every 2 years of the activities that it carries out to verify that those activities comply with these regulations and with its standard operating procedures, by a person who does not have direct responsibility for the activities being audited.

Audits ensure that all regulated activities are performed according to the CTO regulations and the establishment's SOPs. They must address regulated activities that have an impact on CTO safety. All the activities that need to be audited must be reviewed at a minimum every 2 years and there should be an SOP written for these audit activities.

Management must document and review the audit findings and follow-up actions/corrective actions should be implemented in a timely manner. If your establishment has arranged with another establishment to perform any regulated activity on your behalf, you should verify that those activities are being conducted appropriately and comply with the CTO regulations. This should be done every 2 years. For example, you may assess a contractor's compliance by auditing the contractor on-site or remotely or by reviewing audit reports provided by the contractor or by a third party that has audited the contractor.

An establishment should audit all establishments performing regulated activities on its behalf. An establishment contracting another establishment to conduct transmissible disease testing is not required to audit the testing facility if:

- there is an agreement in place that the testing lab will inform the source establishment of any changes to assays used to perform the required tests
- source establishment keeps an up-to-date list of the test kits used on its behalf by the testing lab
- testing laboratories follow the test kit manufacturer's instructions and their own SOPs.
 - the facility should inform the source establishment if any deviation occurs during testing
- the testing facility is accredited by a recognized laboratory accreditation program and the source establishment has a copy of the current accreditation certificate
 - examples include provincial programs such as the Institute for Quality Management in Healthcare (IQMH) program or an international program such as the College of American Pathologists (CAP) Laboratory Accreditation Program

Personnel responsible for carrying out the QA system requirements should conduct the audits. They must know the subject matter and the process being audited. Management must define the responsibilities and who is responsible for and has the authority to conduct the audit. Also,

personnel auditing an activity must not be directly responsible for that activity. For example, a supervisor responsible for donor screening must **not** audit any donor screening activities done in its own facility.

The living donor organ programs should work together to develop standardized SOPs and questionnaires to ensure donor screening and testing practices are consistent among the different organizations.

1.15 Power of inspectors (section 77)

Taking photographs:

77. An inspector may, in the administration of these regulations, take photographs of any of the following:

- a. any article that is referred to in subsection 23(2) of the act
- b. any place where the inspector believes on reasonable grounds that any article referred to in paragraph (a) is processed
- c. anything that the inspector believes on reasonable grounds is used or is capable of being used in the processing of any article referred to in paragraph (a)

An inspector is a person designated under section 22(1) of the *Food and Drugs Act* to enforce the act and regulations. Once designated by the Minister, an inspector will carry out his/her responsibilities according to the guiding principles of transparency and fairness, as described in Health Canada's compliance and enforcement policy. Inspectors' regulatory powers are described under section 23 of the act.

Learn more:

- [Compliance and enforcement policy \(POL-0001\)](#)

Section 23 authorizes inspectors to examine and make copies of documents and records, even if they contain personal medical information. Inspectors review these documents to verify compliance with the CTO regulations. Health Canada handles all information in accordance with applicable laws on privacy, confidentiality and access to information.

Learn more:

- [Health Canada's Access to Information and Privacy Office](#)

1.16 Transitional provisions (section 78)

Processed within 5 years before registration

78. (1) Subject to subsection (2), the following establishments may import, distribute or transplant, as the case may be, cells and tissues that were processed within 5 years before the day on which these regulations are registered:

- a. a registered establishment
- b. a transplant establishment that does not distribute cells or tissues

Prohibition:

(2) An establishment may not import, distribute or transplant, as the case may be, cells or tissues under subsection (1) unless the requirements of subsection 56(2) and section 57 are met.

1.17 Coming into force (section 79)

Six months after registration

79. (1) These regulations, except subsection 26(1), come into force 6 months after the day on which they are registered.

Exception

(2) Subsection 26(1) comes into force 1 year after the day on which these regulations are registered.

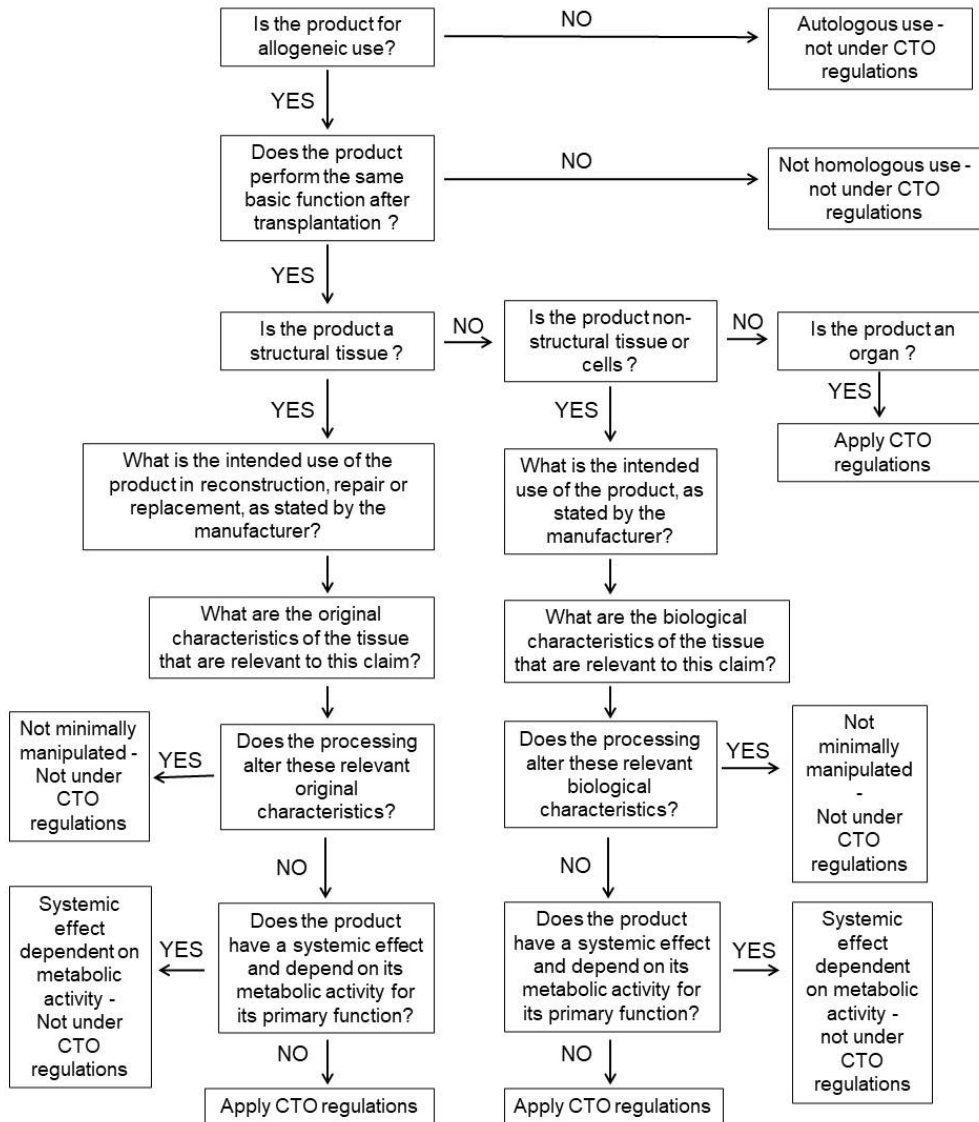
Transitional provision

(3) Section 78 ceases to be in force 5 years after the day on which these regulations are registered.

2 Classification of CTOs

Note: Despite having a systemic effect and being dependent on their metabolic activity for their main function, minimally manipulated lymphohematopoietic cells and islet cells intended for homologous use are regulated under the CTO regulations.

Classification of human cells, tissues, organs or derived products for transplantation



Alt text. This is a decision tree that explains the classification of cells, tissues, and organs.

Long description

Use of this decision tree to help you determine whether a particular tissue or cell product falls under the scope of the CTO regulations.

Step 1: Determine if the product is for allogeneic use or autologous use. A product for **autologous** use does not fall under the scope of the regulations.

Step 2: Determine if the allogeneic product performs the same basic function after transplantation. If it doesn't, then the product is not for **homologous** use and therefore does not fall under the scope of the regulations.

Step 3: Determine if the allogeneic homologous use product is a structural or non-structural product.

For **structural products**, answer these 3 questions to determine how to proceed:

1. What is the intended use of the product in reconstruction, repair or replacement, as stated by the manufacturer?
2. What are the original characteristics of the tissue that are relevant to this claim?
3. Does the processing of the tissue alter these relevant original characteristics?

If processing has altered the relevant original characteristics, the product does not fall under the scope of the regulations. If processing has not altered these characteristics, you must then determine if the product has a systemic effect and depends on its metabolic activity for its primary function. If it does, the product does not fall under the scope of the regulations. If it doesn't, the product does fall under the scope of the regulations.

For **non-structural** products for allogeneic and homologous use, answer these 3 questions to determine how to proceed.

1. What is the intended use of the product as stated by the manufacturer?
2. What are the biological characteristics of the tissue or cells that are relevant to this claim?
3. Does the processing of the tissue or cells alter these relevant biological characteristics?

If processing has altered the relevant biological characteristics, the product does not fall under the scope of the regulations. If processing has not altered these characteristics, you must then determine if the product has a systemic effect and depends on its metabolic activity for its primary function. If it does, the product does not fall under the scope of the regulations. If it doesn't, the product does fall under the scope of the regulations.

3 Testing for infectious diseases

These tables are included for reference only.

For details on testing to assess the suitability of CTO donors, including timeframes, refer to sections 18 to 23 (implementation page) of this guidance document.

Table 3: Tissue donors, except ocular tissues

Appropriate and effective infectious disease markers	Mandatory	Recommended
anti-HIV 1	yes	n/a
anti-HIV 2	yes	n/a
HBsAg	yes	n/a
anti-HBc IgG	yes	n/a
anti-HBc IgM	yes	n/a
anti-HCV	yes	n/a
anti-HTLV-I	yes*	n/a
anti-HTLV-II	yes*	n/a
syphilis	yes	n/a
HIV-1 using NAT	yes**	n/a
HCV using NAT	yes**	n/a
WNV using NAT	n/a	yes

*Mandatory for donors of leukocyte-rich tissue and recommended for donors of tissues that are not considered to be leukocyte-rich.

**Mandatory for tissue from deceased donors. Not necessary for tissue from living donors if the 180-day quarantine and donor retesting protocol is followed.

n/a: not applicable

Table 4: Ocular tissues donors

Appropriate and effective infectious disease markers	Mandatory	Recommended
anti-HIV 1	yes	n/a
anti-HIV 2	yes	n/a
HBsAg	yes	n/a
anti-HBc IgG	yes	n/a
anti-HBc IgM	yes	n/a

anti-HCV	yes	n/a
HIV-1 using NAT	yes	n/a
HCV using NAT	yes	n/a
WNV using NAT	n/a	yes

n/a: not applicable

Table 5: Organ or islet cells donors

Appropriate and effective infectious disease markers	Mandatory	Recommended
anti-HIV 1	yes	n/a
anti-HIV 2	yes	n/a
HBsAg	yes	n/a
anti-HBc IgG	yes	n/a
anti-HBc IgM	yes	n/a
anti-HCV	yes	n/a
anti-HTLV-I	yes	n/a
anti-HTLV-II	yes	n/a
toxoplasmosis	yes*	n/a
syphilis	yes	n/a
anti-CMV IgG	yes	n/a
anti-CMV IgM	n/a	yes
Epstein-Barr virus	yes	n/a
HIV-1 NAT	n/a	yes**
HCV NAT	n/a	yes**
WNV using NAT	n/a	yes

*For heart donors

**HIV-1 NAT and HCV NAT are only recommended for living organ donors and high-risk deceased organ donors whose organs will be exceptionally distributed.

n/a: not applicable

Table 6: Lymphohematopoietic cells donors

Appropriate and effective infectious disease markers	Mandatory	Recommended
anti-HIV 1	yes	n/a
anti-HIV 2	yes	n/a
HBsAg	yes	n/a
anti-HBc IgG	yes	n/a
anti-HBc IgM	yes	n/a
anti-HCV	yes	n/a
anti-HTLV-I	yes	n/a
anti-HTLV-II	yes	n/a
anti-CMV IgG	yes	n/a
anti-CMV IgM	n/a	yes
syphilis	yes	n/a
HIV-1 using NAT	yes*	yes
HCV using NAT	yes*	yes
WNV using NAT	yes	n/a

*Mandatory for banked lymphohematopoietic cell donation (that is, cord blood) only.

n/a: not applicable