Health Canada Santé Canada

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July 29, 2005

05-116401-181

TO: Establishments and individuals involved in the handling and /or processing of human cells, tissues and organs (CTO) for transplantation

RE: Health Canada Directive to Address the Safety of HumanCells, Tissues and Organs for Transplantation

Please find enclosed the documents entitled, *Technical Requirements to Address the Safety of Cells, Tissues and Organs for Transplantation* (*Directive*) and *Safety Requirements for Human Cells, Tissues and Organs for Transplantation* (*Guidance Document*) dated July 2005. These documents are being re-issued by Health Canada to establishments and individuals in Canada involved in the handling and/or processing of human cells, tissues and organs (CTO) for transplantation. These documents replace the *Directive* and *Guidance Document* issued in January 2003. The changes in the *Directive* and *Guidance Document* are concurrent with the mandate of Health Canada; as such, amendments to the *Directive* and *Guidance Document* have been made with the health and safety of Canadians in mind. Electronic copies of these documents can be found on the Health Canada website at the following address: www.hc-sc.gc.ca/hpfb-dgpsa/bgtd-dpbtg/cto_directive_e.html.

With respect to the changes within the *Directive* and *Guidance Document*, particularly noteworthy is the removal of the recognition of other standards as being equivalent to the requirements in the *Directive* and *Guidance Document*. The January 2003 version of the *Guidance Document* stated that other standards used in the community, such as the American Association of Tissue Banks (AATB), would be considered equivalent to the requirements of the *Directive* and *Guidance Document*. The 2005 *Guidance Document* no longer grants that equivalency to any other standard. The

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requirements in the *Directive* and *Guidance Document* must be met for all human cells, tissues and organs for

transplantation that are processed, distributed and imported into Canada.

As with the original documents, the revised *Directive* and *Guidance Document* are based on National Standards for the Safety of Cells, Tissues and Organs for Transplantation and Assisted Reproduction, published by the Canadian Standards Association (CSA). As such, it is important that any issue regarding the applicability or the feasibility of the requirements therein be raised with the CSA. The Standards contain "Proposal for Change" forms. Please submit your comments to the CSA as per the instructions on the forms.

The July 2005 *Guidance Document* is an interim measure until the new regulations regarding the safety of human cells, tissues, and organs for transplantation come into effect. Health Canada strongly recommends that your establishment review this document carefully and make appropriate changes to its standard operating procedures, if required. It is in the best interest of the health and safety of Canadians for every establishment to comply with the *Directive* and *Guidance Document*. Should you have questions regarding the compliance of your establishment with these documents, please contact Health Canada for further guidance as to how to proceed in your particular circumstance.

If you have any questions concerning the *Directive* or *Guidance Document*, please do not hesitate to contact Liz Anne Gillham-Eisen of the Biologics and Genetic Therapies Directorate by e-mail at BGTD_PPD_DPP@hc-sc.gc.ca.

Yours sincerely,

Dr. Pierre J. Charest
A/Director General

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Enclosure:

1) Technical Requirements to Address the Safety of Cells, Tissues and Organs for Transplantation (Directive).

2) Safety Requirements for Human Cells, Tissues and Organs for Transplantation (Guidance Document).

Technical Requirements to Address the Safety of Human Cells, Tissues and Organs for Transplantation (*Directive*)

This *Directive* replaces the Health Canada Directive issued in January 2003.

1. PURPOSE

The purpose of this *Directive* is to advise all establishments and individuals in Canada handling human cells, tissues and organs of the importance of adhering to standards of safety with respect to the processing, distribution and importation of these products for transplantation. This *Directive* applies to those establishments described below in "Scope".

2. BACKGROUND

The therapeutic use of human cells, tissues and organs can enhance the quality and duration of life. Health Canada is the federal authority which regulates the safety, efficacy and quality of therapeutic products used in Canada, pursuant to the *Food and Drugs Act.* Health Canada works with provincial and territorial governments, other regulatory agencies, trade associations, health professionals and their associations and the Canadian public to fulfill its mandate.

Some cells and tissues are regulated under the *Food and Drugs Act.* For example, human semen used for assisted conception is regulated under its own set of regulations under the *Food and Drugs Act*, namely, the *Processing and Distribution of Semen for Assisted Conception Regulations*. Demineralized bone, heart valves and dura mater, are regulated as medical devices under the *Medical Devices Regulations*. Other human tissues, such as blood, are being regulated as drugs under the *Food and Drug Regulations*.

3. CURRENT STATUS

Health Canada is developing a new regulatory framework under the *Food and Drugs Act* for cells, tissues and organs which will be informed by the National Safety Standards that were developed and published by the Canadian Standards Association in summer 2003. Other key elements of the regulatory framework will include adverse event reporting and a compliance monitoring and enforcement strategy. The proposed regulatory framework will be aimed at maximizing the safety of human cells, tissues and organs available for therapeutic purposes.

Until the new regulatory framework is in place, Health Canada is recommending that establishments and individuals in Canada handling and/or processing human cells, tissues and organs adhere to the provisions of the *Safety Requirements for Human Cells, Tissues and Organs for Transplantation* (*Guidance Document*) herein with respect to the processing, distribution and importation of these products for transplantation. The attached *Guidance Document* sets out safety requirements with respect to donor suitability assessment and the collection/retrieval, processing, preservation, packaging, labelling, storage, quarantining, record keeping, distribution, importation, adverse event reporting, investigation and recall of cells, tissues and organs for transplantation.

Cells, tissues and organs that are not processed in accordance with the standards of safety specified in the attached *Guidance Document* raise a risk of being unsafe and of being manufactured, prepared, preserved, packaged or stored under unsanitary conditions; being adulterated or of having the potential to cause injury under normal conditions of use.

Consequently, in order to protect the health and safety of Canadians, where evidence shows that cells, tissues and organs are not processed in accordance with the *Guidance Document*, Health Canada will exercise its authority under Sections 8 and 19 of the *Food and Drugs Act* to prohibit the distribution of such products.

4. SCOPE

4.1

This *Directive* applies to human organs, and minimally manipulated human cells and tissue used in transplantation procedures. Minimal manipulation of cells and tissues is defined as:
a) in respect of a structural tissue, processing that does not alter the original characteristics that are relevant to its claimed utility for reconstruction, repair or replacement;
b) in respect of cells and nonstructural tissue, processing that does not alter the relevant biological characteristics of cells or tissues.

No person shall distribute, import or make available a cell, tissue or organ for transplantation unless the cell, tissue or organ has been processed or distributed in accordance with this *Directive* and the attached *Guidance Document*.

4.2

This *Directive* applies to establishments handling human cells, tissues or organs, which are involved in any of the following activities:
a) processing (as defined in the *Guidance Document*)
b) importation
c) distribution
d) transplantation

4.3

This *Directive* does not apply to :
a) cells, tissues and organs that are for autologous use;
b) cells, tissues and organs that are for non-homologous use;
c) cells, tissues and organs that are used in investigational testing involving human subjects under Part 3 of the *Medical Devices Regulations* or clinical trials under Division 5 of Part C of the *Food and Drug Regulations*;
d) Class IV medical devices that are regulated under the Medical Devices Regulations, for example heart valves, dura mater and demineralized bone;
e) whole blood, blood components and blood products, except for cord blood;

f) cells and tissues that are regulated under the *Assisted Human Reproduction Act* or any of its regulations; and
g) semen that is regulated under the *Processing and Distribution of Semen for Assisted Conception Regulations*.

5. ADDITIONAL INFORMATION

Additional Information on Health Canada's proposed new regulatory framework for cells, tissues and organs can be found at:

www.hc-sc.gc.ca/hpfb-dgpsa/bgtd-dpbtg/cto_directive_e.html

Questions concerning this *Directive* should be referred to:

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Health Canada Santé Canada

Guidance Document

Basic Safety Requirements for Human Cells, Tissues and Organs for Transplantation

Health Products and Food Branch

July 2005

Canada

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1. ABBREVIATIONS AND EXPLANATORY NOTE

AIDS	Acquired Immuno-Deficiency Syndrome
CJD	Creutzfeldt-Jakob Disease
CMV	Cytomegalovirus
EBV	Epstein-Barr Virus
HBc	Hepatitis B Core
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA	Histocompatibility
HTLV	Human T-cell Lymphotropic Virus
IgG	Immune Globulin G
IgM	Immune Globulin M
ODO	Organ Donation Organization
SOPs	Standard Operating Procedures

In this *Guidance Document*, "shall" is used to express a requirement, i.e., a provision that the user is obliged to satisfy; "should" is used to express a recommendation or that which is advised but not required; and "may" is used to express an option or that which is permissible within the limits of the *Guidance Document*. Notes accompanying clauses do not include requirements or alternative requirements; the purpose of a note accompanying a clause is to separate from the text explanatory or informative material.

2. DEFINITIONS

Accident—any occurrence, not associated with a deviation from standard operating procedures (SOPs), or applicable laws and regulations. An accident may occur during donor suitability assessment, retrieval, processing, preservation, packaging, labelling, storage, quarantine, evaluation, recordkeeping, adverse event reporting, distribution, importation or exportation, and recall of cells, tissues and organs. Such accidents may affect the performance, biocompatibility, or freedom from transmissible pathogens of the cells, tissues and organs or the ability to track cells, tissues and organs to the donor or recipient.

Adverse event—any unintended or untoward medical occurrence that may be consequent or related to cells, tissues or organs that are transplanted. An adverse event may be considered to be an incident or a reaction.

Container—a receptacle that is used to contain cells, tissues or organs and is in direct contact with the cells, tissues or organs.

Donor screening—the process for determining the suitability of a specific individual for cell, tissue, or organ donation based on medical, social, and sexual history, physical examination and autopsy finding (if an autopsy was performed).

Donor suitability assessment—the process for determining the suitability of a specific individual for cell, tissue or organ donation based on donor screening and donor testing.

Donor testing—the process for determining the suitability of a specific individual for cell, tissue or organ donation based on laboratory tests on a specimen collected from the donor to determine past or present infection with a relevant infectious disease or the presence of a genetic defect.

Error—a departure from the SOP or applicable laws and regulations during donor suitability assessment, retrieval, processing, preservation, packaging, labelling, storage, quarantine, evaluation, recordkeeping, adverse event reporting, distribution, importation or exportation, and recall of cells, tissues, or organs that may cause infectious disease transmission, adversely affect the clinical performance of cells, tissues, or organs, or interfere with the ability to track cells, tissues, or organs to the donor.

Exceptional release—the release of cells, tissues or organs to a transplant program from a donor in whom the donor suitability assessment has identified an increased risk for disease transmission.

Identification number—a unique numeric or alphanumeric designation assigned to, and thus associated with, a donor or recipient, a specific establishment and cells, tissues or organs, for the purpose of tracking and confidentiality. If donated cells, tissues and organs are divided, the unique donor identification number is distinctly associated with each part.

Importer—an establishment or individual that receives cells, tissues or organs from a foreign country.

Insert— the material/paperwork accompanying the cells, tissue or organ that contains information about the graft, directions for use (including safe use), additives and warnings.

Label — any legend, word, or mark attached to any cell, tissue, organ or package.
Note: *Labels may include, for example, instructions for safe use, a list of additives, or warnings.*

Organ Donation Organization (ODO) — an organization or agency with the responsibility for the facilitation of cell, tissue or organ donation, retrieval and distribution that includes, but is not limited to, receiving referrals of cells, tissues or organs for donation; collecting the information necessary to determine the suitability of the donor and his or her cells, tissues or organs; offering the cells, tissues or organs to the appropriate transplant program; coordinating the retrieval of the cells, tissues or organs; preserving, storing, transporting, releasing and delivering the cells, tissues or organs to the transplant program; and documenting this process.

Note:
1) *ODO services may include research activities*.
2) *Tissue donation organizations may fulfill the same responsibilities as an ODO*.
3) *The term "organ donation organization" is used in this Guidance Document in place of the term "organ procurement organization"*.

Package—any carton, receptacle or wrapper, including the label, container and contents of a container.

Processing—in respect of cells, tissues and organs, means any of the following activities:
a) donor screening;
b) donor testing;
c) donor suitability assessment;
d) retrieval;

e) post-retrieval testing;
f) preparation for use in transplantation;
g) preservation;
h) quarantine;
i) banking; and
k) labelling and packaging.

Quality assurance (QA)—part of coordinated activities to direct and control the activities of an establishment with regard to quality and to focus on providing confidence that quality requirements are being fulfilled.

Quarantine—the identification of cells, tissues and organs that are not suitable for use or that have not yet been characterized as being suitable for use. Includes storage in an area clearly identified for controlled sequestration and other procedures that prevent the release of such cells, tissues and organs.

Recipient—any individual who receives a cell, tissue or organ transplantation.

Serious adverse event—an adverse event in a recipient of a transplant that:
a) results in in-patient hospitalization;
b) results in prolongation of existing hospitalization;
c) results in persistent or significant incapability (including transmission of a disease or failure of the transplant's function or integrity);
d) is life threatening; or
e) results in death.

Source establishment—the ODO or the establishment involved in processing cells, tissues or organs from living or cadaveric individuals.

3. QUALITY MANAGEMENT

3.1 Quality Assurance

Each establishment shall establish, maintain and document quality assurance activities to ensure all policies, procedures, processes, products and services of the establishment conform to its Standard Operating Procedures (SOPs), this *Guidance Document* and applicable laws and regulations.

3.2 Standard Operating Procedures (SOPs)

3.2.1

Each establishment shall maintain SOPs. The SOPs shall include a detailed description of the following:
a) the procedures used for:
   i) donor suitability assessment;
   ii) the retrieval, processing, preservation, packaging, labelling, storage, quarantine, evaluation distribution, importation or exportation and recall of cells, tissues and organs; and
   iii) record keeping, adverse event reporting and notification.
b) the procedures used for establishment maintenance and cleaning and environmental monitoring;

c) the procedures used for equipment maintenance, cleaning, calibration and validation;
d) investigation of complaints;
e) copies of publications cited in support of the policies and procedures;
f) a description of the tests, procedures and tolerance limits applied; and
g) quality control activities.

3.2.2

Cells, tissues and organs shall be processed and preserved according to the SOPs.

3.3 Process Control

All processes shall be validated prior to implementation, revalidated whenever significant changes are made in the method or material being analyzed and when deviations from a validated process occur.

3.4 Investigations

Designated personnel shall investigate and document all errors, accidents, complaints, adverse events and recalls. The documentation shall include the nature of the event, the corrective actions recommended and implemented, the date and the personnel involved.

4. RECORD KEEPING AND TRACKING

4.1 Record Keeping Requirements

4.1.1

Records shall be confidential, accurate, complete, legible and indelible.

4.1.2

The records shall provide a complete history of each donated cell, tissue or organ and shall cover all activities from informed consent and donor suitability assessment to the final disposition of the cells, tissues or organs.

4.1.3

All laboratory results and other tests used to determine the final release of cells, tissues or organs shall be maintained by the processor and distributor.

4.1.4

All manual transcription of test results shall be independently verified.

4.1.5

The donor record shall include:
a) the donor identification number;

b) documentation of each significant step in the donor suitability assessment;
c) documentation of donor testing for infectious disease;
d) documentation of notification, retrieval, labelling, processing, preservation, packaging, evaluation, storage, quarantine and distribution;
e) the identity of the person(s) performing the work and the dates of the various entries;
f) the test results and interpretation of the test results;
g) a complete history of the work performed to enable tracking of records to the particular cells, tissues and organs involved;
h) documentation of adverse events, problems, complaints, corrective actions, deviations from SOPs and product deficiencies;
i) the date and personnel involved in each phase of the process, i.e., from the time of donor screening and cell, tissue or organ retrieval to the final disposition of the cells, tissue or organ;
j) the donor log, where applicable; and
k) the destruction or other disposition of unsuitable or unused cells, tissues or organs.

4.2 Tracking (Traceability) Requirements

4.2.1

Each establishment involved in the retrieval, processing, distribution or storage of cells, tissues or organs shall have an identification number that allows for the tracking of cells, tissues or organs from the donor source to the recipient and vice versa and, if applicable, the tracking of archived serum samples and quality control specimens to the donor. All establishments handling the cells, tissues or organs shall ensure that their donor identification number matches the donor identification number of the establishment from which it acquired the cells, tissues or organs.

4.2.2

Each establishment involved in transferring or distributing cells, tissues or organs to other establishments shall have mechanisms in place to ensure communication between itself and those establishments for the purpose of tracking cell, tissue or organ donations from the donor to all consignees, as well as for the purposes of notification and recall. Consignees shall have mechanisms in place to permit the tracking of all recipients of cells, tissues and organs retrieved from a single donor.

4.2.3

Each establishment involved in the transplantation of cells, tissues and organs shall be able to identify the link to the recipient by a unique identification number (i.e., the recipient's transplant/medical/dental record shall include the donor identification number and the type of cell, tissue or organ transplanted).

4.2.4

Establishments shall keep accurate records of:
a) the distribution of all cells, tissues and organs, according to the donor identification number;
b) the type of cells, tissues or organs;
c) the donor identification number;
d) the personnel involved in procedures;
e) the identification of the recipient;

f) the dates of retrieval and transplantation;
g) the date of transplant and outcomes, where applicable.

5. DONOR SUITABILITY ASSESSMENT

5.1 General

Donor consent should be obtained according to applicable laws.

5.2 Suitability of Donors

5.2.1

The suitability of a specific individual for cell, tissue or organ donation shall be documented and shall be based on medical and social history, clinical status, physical examination, tests and autopsy (if performed).

5.2.2

A medical/sexual/psychosocial questionnaire shall be used for donor screening. The questionnaire shall include, but will not be limited to, questions to evaluate all of the general and specific contraindications/exclusion criteria set out in section 5.5.1 of this *Guidance Document*. The questionnaire shall be completed for each donor and will indicate the response for each question.

5.3 Documentation

Documentation of the donor suitability assessment shall include the following:
a) donor's name, address, identification number and date of birth;
b) date(s) of the interview;
c) completed donor consent form(s);
d) name of the healthcare professional who administered the questionnaire(s) and reviewed the medical records;
e) donor's medical records, if available;
f) date and results of physical examination;
g) completed medical, sexual, and social history questionnaire and date of completion;
h) dates and results of laboratory tests and, if applicable, the interpretation of the results;
i) hemodilution assessment, if required, accompanied by a statement indicating whether the donor received any transfusions or infusions prior to obtaining the blood sample for testing; and
j) donor log, if applicable.

5.4 Medical History

5.4.1 Perfusable Organ-Specific Requirements

5.4.1.1

For living and deceased donors, a donor history shall be obtained from all available medical sources, as well as the next of kin. This shall include the following:

a) any history of malignancy or tuberculosis or other communicable disease;

b) any history of other major illnesses, previous hospitalizations, previous surgical procedures, previous blood or blood-product transfusions, current medications and any drugs administered within the previous 48 hours;
c) any history of disease or abnormality of any of the consented organs or tissues;
d) previous residence or travel.

5.4.1.2

Additional requirements for cadaveric donors include:
a) the cause of death;
b) any episode affecting hemodynamic stability since the onset of critical illness, the treatment history and most recent status;
c) for a donor infant less than 18 months of age, a maternal history that includes:
    i) history of tuberculosis, hepatitis or other communicable disease;
    ii) any high-risk behaviour for HIV [see section 5.5.1.1(g) for reference]; and
d) any history of sepsis since the onset of critical illness, its documentation (culture report) and treatment.

5.4.2 Lymphohematopoietic Cell-Specific Requirements

The donor's medical history shall include at least the following:
a) vaccination history;
b) travel history;
c) blood transfusion history;
d) pregnancy assessment for all female donors of childbearing potential; and
e) questions to identify persons at high risk for significant transmissible infections according to the authority having jurisdiction for donors of lymphohematopoietic cells.

5.5 Donor Screening

5.5.1 Contraindications or Exclusion Criteria

5.5.1.1 General

Examples of contraindications or exclusion criteria to donation of all cells, tissues and organs include, but are not limited to, the following:
a) death from an unknown cause;
b) death with neurological disease of an unestablished etiology (e.g., Alzheimer's, multiple sclerosis, Parkinson's, amyotrophic lateral sclerosis (ALS);
c) prion-related disease [e.g., Creutzfeldt-Jakob disease (CJD), family history of CJD, recipients of human-derived pituitary growth hormone or dura mater];
d) subacute sclerosing panencephalitis;
e) progressive multifocal leukoencephalopathy;
f) rabies;
g) high risk for human immunodeficiency virus (HIV);

Note: *The exclusionary criteria for HIV risk behaviours are outlined in the CAN/CSA-Z900.1-03, Cells, Tissues, and Organs for Transplantation and Assisted Reproduction: General Requirements, Annex E, "Exclusionary Criteria for Human Immunodeficiency Virus (HIV) Risk Behaviours"*.

h) persons with repeatedly reactive screening assays or who test positive for
   i) antibody to HIV types 1 or 2 (anti-HIV-1 or anti-HIV-2);
   ii) hepatitis B surface antigen (HBsAg);
   iii) antibody to hepatitis C virus (anti-HCV); or
   iv) antibody to human T-cell lymphotropic virus types I or II (anti-HTLV-I or anti-HTLV-II);
i) active systemic bacterial, fungal or viral infection;
j) leukemias and lymphomas.

5.5.1.2 Tissue-Specific Requirements

In addition to the contraindications or exclusion criteria listed in section 5.5.1.1, exclusion criteria for tissue donors include, but are not limited to, the following:
a) active viral encephalitis or encephalitis of unknown origin;
b) malaria; and
c) tuberculosis.

5.5.1.3 Ocular Tissue-Specific Requirements

5.5.1.3.1

In addition to the contraindications or exclusion criteria listed in section 5.5.1.1, contraindications for tissues used for penetrating keratoplasty, lamellar or patch grafts, epikeratoplasty and for scleral tissues include, but are not limited to, the following:

a) congenital rubella;
b) Reye's syndrome;
c) active viral encephalitis or encephalitis of unknown origin or progressive encephalopathy;
d) active bacterial or fungal endocarditis;
e) active viral hepatitis;
f) intrinsic eye disease such as
   i) retinoblastoma;
   ii) malignant tumours of the anterior ocular segment, of primary or metastatic origin (e.g., adenocarcinoma);
   iii) active ocular or intraocular inflammation;
   iv) congenital or acquired disorders of the eye that would preclude a successful outcome for the intended use; or
   v) pterygia or other superficial disorders of the conjunctiva or corneal surface involving the central optical area of the corneal button;
g) active disseminated lymphomas; and
h) prior intraocular or anterior segment surgery such as,
   i) refractive corneal procedures; and
   ii) laser photoablation surgery.

Note: *Corneas from patients with anterior segment surgery may be used if they are screened by specular microscopy and meet the eye bank's endothelial cell count standards as outlined in the SOPs. Retinal and panretinal photocoagulation may be considered following clearance from the Medical Director.*

5.5.1.3.2

Notwithstanding the contraindications specified in section 5.5.1.3.1 (f) and (h), tissues may be transplanted if deemed acceptable for a specific use by the Medical Director.

5.5.2 Physical Examination

A physical examination of the donor must be performed by a qualified person to assess any evidence of high-risk behaviour, signs of malignancy, bacterial or viral infection and trauma to the retrieval site.

5.6 Testing

5.6.1 General

5.6.1.1
The SOPs shall describe the tests and procedures required for measuring, assaying or monitoring properties of cells, tissues and organs essential to the evaluation of their safety for transplantation.

5.6.1.2

Testing shall be performed by a laboratory that meets applicable laws and regulations, or in the case of imported cells, tissues and organs, by a laboratory that meets current requirements of the donor centre of origin.

5.6.1.3

Testing of donor blood for specified infectious agents shall be performed with in vitro diagnostic devices that comply with federal regulatory requirements. The manufacturer's instructions for the performance and interpretation of its test shall be followed. Blood donor screening tests should be used. Where Nucleic Acid Tests (NAT) are available for blood donor screening, they should be used in addition to the required serological tests.

5.6.1.4

For the testing of donors where only cadaveric blood is available, establishments should use a test that is specifically licensed or authorized for the testing of cadaveric blood.

5.6.1.5

Where test kits that comply with federal regulatory requirements are not available for a test specified in this Guidance Document, the laboratory specified in section 5.6.1.2 should ensure that all tests used for the evaluation of the safety of cells, tissues and organs are validated to support the use of the method for the intended applications.

5.6.1.6

Test results shall be documented in the donor record.

5.6.2 Procedures for Serological Screening Tests for Infectious Diseases

5.6.2.1 General

Serological tests for infectious diseases specified in 5.6.4 shall be performed and interpreted according to manufacturer specifications.

5.6.2.1.1

Cells, tissues or organs may be released for transplantation if the donor's blood sample is reactive for a nontreponemal screening test for syphilis but negative for a treponemal-specific confirmatory test.

5.6.2.2 Tissue-Specific Requirements

Results of the infectious disease tests specified in section 5.6.4 are acceptable if performed on a blood specimen taken within 7 days prior to donation for deceased donors and within 30 days of donation for living donors.

5.6.2.3 Perfusable Organ-Specific Requirements

For living donors, the infectious disease tests specified in section 5.6.4 shall be performed on a blood specimen taken within one month prior to the surgery. The minimum testing required at the transplant centre for the anesthetic and operative procedure shall be performed.

Note: *It is recommended that living donors be retested at the time of donation, even if the results are not available before the time of transplantation.*

5.6.2.4 Lymphohematopoietic Cell-Specific Requirements

The infectious disease tests specified in section 5.6.4 shall be performed within 30 days prior to collection (unless a previously positive test has been documented). In the event that collections from the same donor are performed more than 30 days apart, donors shall be retested for the infectious disease agent and markers.

5.6.2.5 Archived Cell, Tissue, Organ or Serum Samples

It is recommended that cell, tissue or blood samples be collected from the donor for future testing, where related to the safety of transplantation (e.g., for future testing when new serological tests for existing or new pathogens are adopted for donor screening). Cell, tissue, organ or serum samples shall be stored frozen.

5.6.3 Minimum Serological Testing for Infectious Diseases

5.6.3.1 General

Minimum donor serological testing shall include the following:

a) anti-HIV-1, and anti-HIV-2;
b) HBsAg;
c) anti-HCV.

5.6.3.2 Tissue-Specific Requirements

In addition to 5.6.4.1 donors shall be tested for:

d) anti-HTLV-I and anti-HTLV-II;
e) syphilis.

Note: *It is recommended that donors of tissues subject to the living donor quarantine requirements also be tested for total antibody to hepatitis B core (total anti-HBc, i.e., IgM and IgG) to prevent the processing and storage of tissues from donors who are positive for these markers.*

5.6.3.3 Perfusable Organ-Specific Requirements

In addition to the tests specified in section 5.6.4.1,

a) donors shall be tested for:
   i) total anti-HBc, and
   ii) toxoplasmosis for heart donors, which may be done retrospectively. The presence of toxoplasmosis and the risk of transmission of this disease shall be screened by testing for the presence of toxoplasmosis antibody in the donor's serum using a medically acceptable test (e.g., enzyme-linked immunoassay test); and
   iii) syphilis (note: syphilis testing for organ donors is only mandatory if the organs are not stored in a culture media at 4°C or below for more than 24 h).

b) it is recommended that donors also be tested for:
   i) antibody to cytomegalovirus (anti-CMV IgG and anti-CMV IgM);
   ii) Epstein-Barr virus (antibody to EBV, anti-EBV nuclear antigen (anti-EBNA) IgG, or anti-viral capsid antigen (anti-VCA) IgG), particularly for negative potential recipients.

5.6.3.4 Lymphohematopoietic Cell-Specific Requirements

In addition to the tests specified in section 5.6.3.1 donors shall be tested for:

a) anti-HTLV-I and anti-HTLV-II;
b) syphilis;
c) anti-CMV.

5.6.3.5 Living Donor Tissue Quarantine

Allograft tissues from living donors that are going to be stored shall be held in quarantine for at least 180 days, at which time the donor shall be retested for:

a) anti-HIV-1 and anti-HIV-2;
b) anti-HBc (IgG or total);
c) anti-HCV.

Note: *Postquarantine testing before release of tissues from infant donors may require surrogate testing, as described in Clause 5.6.3.6.*

5.6.3.6 Fetal or Infant Donors

To address possible vertical transmission of infectious agents in donors under 18 months of age, or up to 12 months beyond breast-feeding, the birth mother shall also be tested for total anti-HBc, in addition to tests specified in section 5.6.3 as applicable.

5.6.4 Transfusions and Hemodilution

5.6.4.1

Testing shall be performed on a pre-transfusion/infusion blood sample taken as near to the time of retrieval as possible. If no such sample is available, benchmarks for hemodilution shall be applied.

5.6.4.2

It is recommended that testing be done on the most recent pretransfusion/infusion specimen for which identity and quality can be ensured.

5.6.5 Bacteriological Testing

5.6.5.1 Tissue-Specific Requirements

Bacteriological testing of tissues intended for transplantation shall be performed as follows:

a) Representative bacteriological cultures from each excised tissue (e.g., swab culture or tissue biopsies) shall be obtained aseptically into appropriate culture media or transport medium at the time of retrieval. These cultures shall be taken before the tissue is exposed to any antibiotic-containing preparations.

b) Representative tissue shall be cultured after secondary sterilization procedures according to the SOP for each tissue.

c) Cultures shall be performed for both aerobic and anaerobic organisms, according to approved protocols, so that both rapid- and slow-growing organisms will be detected.

d) Tissues showing bacterial contamination at the time of retrieval may be transplanted if a suitable protocol for disinfection is in place. Organisms shall be identified to the genus level, and the tissue shall be disinfected, either while in process or in a terminal sterilization event, before transplantation is done.

e) If gram negative pathogens are cultured, the tissue shall not be released for transplantation unless it is effectively secondarily sterilized according to validated protocols.

f) When culture results of certain tissues are not available by the time of transplantation (e.g., fresh osteochondral allografts that, because of tissue viability issues, must be transplanted promptly), the results shall be forwarded to the end-user physician as soon as they become available.

g) Each processing step in which tissue is unwrapped and rewrapped shall require repeat bacteriological cultures to rule out contamination during the procedure.

h) Tissue shall be discarded if the final culture results are positive.

5.6.6 Other Tests

5.6.6.1 Blood Typing

Donor blood type (A, B, AB, O), Rh factor and histocompatibility (HLA) typing shall be required, where clinically indicated, for donation of applicable cells, tissues and organs. The tests for donors of lymphohematopoietic cells shall also include HLA-A, B, DR typing and appropriate red cell compatibility with the recipient.

5.6.6.2 Perfusable Organ-Specific Requirements

5.6.6.2.1

General tests shall determine the following:

a) height;
b) weight;
c) ABO blood type;
d) complete blood count (CBC);
e) levels of serum electrolytes;
f) levels of creatinine; and
g) chest X-ray.

5.6.6.2.2

At a minimum, the following tests shall be performed for potential specific organ donors:

a) Kidney: serum electrolyte testing, urea testing, urinalysis and creatinine;
b) Heart: chest X-ray; electrocardiogram (ECG) and 2D echocardiography;
c) Lungs: chest X-ray, pO_2 on 100% oxygen after being on partial end-expiry pressure (PEEP) at 5 cm H_2O for 15 min and tracheal aspirate for gramstain.
d) Liver: bilirubin testing, either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and either prothrombin time (PT) or International Normalized Ratio (INR).
e) Pancreas: blood sugar and amylase.

5.6.6.3 Ocular Tissue-Specific Requirements

5.6.6.3.1 Gross Examination

The corneal-scleral rim shall be initially examined grossly for clarity, epithelial defects, foreign objects, contaminations and scleral colour, e.g., jaundice.

5.6.6.3.2 Slit-Lamp Examination

The cornea shall be examined for epithelial and stromal pathology and in particular, endothelial disease. Enucleated whole globes shall be examined in the laboratory prior to distribution and/or corneal excision. If in situ corneal excision is performed, examination of the donor eye anterior segment with a penlight or portable slit-lamp shall be required. After corneal excision, the corneal-scleral rim shall be evaluated by slit-lamp biomicroscopy, even if the donor eye has been

examined with the slit-lamp prior to excision of the corneal-scleral rim, to ensure that damage to the corneal endothelium or surgical detachment of Descemet's membrane did not occur.

5.6.7 Notification

5.6.7.1

Positive or reactive transmissable disease test results, either confirmed or discordant, obtained from either a living or deceased donor shall be reported to the appropriate health authorities in accordance with federal, provincial and territorial requirements. Positive, reactive or discordant test results shall be immediately reported to all organ donation organizations, tissue and cell banks and transplant programs in receipt of cells, tissues or organs from the donor.

5.6.7.2

Living donors shall be notified of all confirmed positive results.

5.6.7.3

For deceased donors, the donor program shall inform the donor's physician of record prior to death, or the physician who signed the death certificate, of confirmed positive test results.

6. RETRIEVAL, PROCESSING, PRESERVATION AND STORAGE

6.1 General

6.1.1

All nondisposable surgical instruments, devices and supplies used for retrieval, processing and preservation shall be cleaned, disinfected and/or sterilized between donations, as described in the SOP, to prevent contamination and cross-contamination.

6.1.2

Protocols shall be developed, implemented and documented for the validation or qualification of significant products of facilities, processes, equipment, reagents, labels, containers, packaging materials and computer systems.

6.1.3

The establishment shall validate and document methods, time limits, and environmental conditions to maintain the integrity of cells, tissues and organs and to prevent contamination. These shall include time limits, environmental conditions and acceptable temperature ranges for retrieval, processing, preservation, storage and transportation (if applicable).

6.1.4

The SOPs shall describe:

a) the storage temperatures and environmental conditions for all cells, tissues and organs and the procedures to follow in case of power failure or other errors or accidents during storage;
b) procedures to follow when cells, tissues or organs are exposed to environments outside of recommended storage limits; and
c) methods to prevent cross-contamination between cells, tissues and organs.

6.1.5

Reagents used in the collection, processing, preservation and storage shall be of appropriate grade for the intended use and shall be sterile. If commercially prepared devices or reagents are not available and in-house devices or reagents are used, the procedures for their production shall be validated.

6.1.6

The concentration of the reagents used (e.g., cryoprotectant, isotonic solutions, antibiotics, disinfectants) and the acceptable residual amount of reagent shall be documented in the SOP manual.

6.2 Pooling

6.2.1

Pooling of cells and tissues from multiple donors is allowed only in cases where it is required to obtain a therapeutic dose for a single recipient. Pooling of cells and tissues shall be documented in the SOP.

6.2.2

Lymphohematopoietic cells may be pooled from different sources from the same donor (e.g., marrow and peripheral blood). Pooling of lymphohematopoietic cells shall be documented in the SOP.

6.3Retrieval

6.3.1

Time constraints for postmortem retrieval and the appropriate temperature for holding a donor until retrieval shall be determined and documented in the SOP of the retrieving establishment.

6.3.2

Cells, tissues and organs shall be retrieved using aseptic techniques and preserved within time intervals for the retention of biologic functions, in a way that is compatible with the intended use of the cells, tissues and organs.

6.3.3

Each donation shall be documented and a record retained by the donor retrieval establishment. The records shall include the following:

a) the name, address and identification number of the retrieving establishment;
b) documentation of informed consent;
c) the donor's name, age, sex and identification number;
d) the type of reagents, lot number, expiration date and manufacturer of the reagents and supplies used;
e) a description of and identification number for all cells, tissues or organs retrieved;
f) the date and time of retrieval;
g) the names of staff involved in retrieving the cells, tissues or organs; and
h) the disposition and recipient identification number of all cells, tissues or organs retrieved.

6.4 Processing and Preservation

Records of processing and preservation shall include the following:

a) the donor identification number, time and date of receipt of cells, tissues or organs from the retrieval establishment and documentation of the storage conditions, if applicable;
b) the cell, tissue or organ identification number and type of cells, tissue or organ being preserved;
c) the date, time of processing and preservation;
d) the names of the personnel involved in the procedures;
e) the cell, tissue or organ measurements;
f) any observed defects in the cells, tissues or organs;
g) the expiration date and time;
h) a description of any cells, tissues or organs sampled for testing/validation;
i) the results of microbiological tests (e.g., cultures);
j) the establishment identification number;
k) the recipient identification numbers;
l) the disposition of all cells, tissues or organs processed or preserved;
m) the type, lot number, manufacturer and expiration date of supplies and reagents used to process and/or preserve the cells, tissues or organs;
n) the residual amounts of additive (e.g., antibiotics), if applicable; and
o) the residual moisture content, if applicable.

6.5 Packaging, Containers and Storage

6.5.1

All materials that come into contact with the cells, tissues or organs shall be sterile. The establishment shall determine that containers and packaging materials used in the retrieval, processing, preservation and storage of cells, tissues and organs are for the intended purpose, as defined in the SOPs.

6.5.2

Containers and packaging materials shall maintain the integrity, quality, function and sterility of cells, tissues and organs for the entire shelf life, and shall not produce toxic residues during storage. Methods and materials to prevent or indicate the occurrence of tampering should be applied.

6.6 Labels, Inserts and Accompanying Documentation

6.6.1 General

Cells, tissues and organs shall be labelled for identification and tracking during all phases of retrieval, processing, preservation, storage and distribution. The donor identification number (see Clause 4.2.1) shall be included on the identification label of the cells, tissues or organs to facilitate donor/recipient tracking.

6.6.2 Information Requirements

The label and/or insert should identify if appropriate and applicable:

a) the name and identification number of the cells, tissues or organs;
b) the name and address of the establishment of origin of the cell, tissue or organ donation;
c) the donor identification number;
d) date of collection/retrieval;
e) the date of screening and testing of the donor;
f) the specimens tested;
g) the serological and microbiological tests performed and, if necessary, the interpretation of the test results; and
h) any special instructions for storage and handling.

6.6.3 Additional Requirements

In addition to the information requirements specified in section 6.6.2, the label and/or insert should include the following if appropriate and applicable:

a) the name and address of the importer and tissue distribution intermediaries;
b) date and time of death;
c) the volume, size, number of cells and a description;
d) date of cryopreservation or date and time of preservation;
e) the cryoprotectant used and concentration;
f) the type and amount of antibiotic used;
g) the presence of known sensitizing agents;
h) the results of tissue analysis;
i) blood types and Rh factor;
j) the expiry date;
k) the sterilization procedure used;
l) the preservative used and their concentration;
m) the amount, size, dimensions, weight and/or anatomical details of the tissue;
n) name and quantity of perfusion solution used;
o) date and time of aortic clamping for organ donations;
p) instructions for maintaining recipient tracking;

q) instructions for adverse event reporting;
r) biohazard label, if applicable; and
s) recommended storage temperature.

6.6.4 Containers

Containers shall be labelled so as to identify the cell, tissue or organ name and the cell, tissue or organ identification number.

6.6.5 Imported Cells, Tissues and Organs

For imported cells, tissues or organs, the outer shipping container shall display clearly, on the outside surface of that container:

a) the name and business address of the establishment of origin of the cell, tissue or organ donation;
b) type of cell, tissue or organ;
c) name, address and telephone number of the Canadian importer;
d) recommended storage conditions; and
e) a declaration signed by the foreign establishment of origin, or its authorized agent, certifying that the cell, tissue or organ has been processed in accordance with the requirements specified in this *Guidance Document*.

7. QUARANTINE AND RELEASE

7.1 General

Cells, tissues and organs shall be quarantined until:

a) donor suitability assessment has been completed (see Sections 5.1 to 5.5);
b) infectious disease testing has been completed and found to be negative (see Section 5.6);
c) compliance with quality control tests and procedures has been demonstrated; and
d) investigation of errors or accidents has been completed.

7.2 Exceptional Release

7.2.1

A source establishment may offer cells, tissues and organs for exceptional release that have not been processed in accordance with this *Guidance Document* if the following conditions are met:

a) the transplant physician or dentist justifies the request based on their clinical judgment, and requests their medical director to authorize the exceptional release;
b) the medical director of the transplant establishment authorizes the exceptional release; and
c) the transplant establishment obtains the informed consent of the recipient.

7.2.2

A source establishment that distributes cells, tissues or organs under section 7.2.1 shall put a notice of exceptional release in its record.

7.2.3

A transplant establishment that authorizes the exceptional release of cells, tissues or organs under 7.2.1 shall put a notice of exceptional release in its record and send a copy of the notice to the source establishment.

7.2.4

A notice of exceptional release shall contain all of the following information:

a) the provisions of this *Guidance Document* with which the cell, tissue or organ is not in compliance at the time of its release;
b) the justification for the release that formed the basis for the medical director's decision to authorize it;
c) the name of the source establishment that distributed the cell, tissue or organ;
d) the name of the transplant establishment, of the transplant physician or dentist and of the medical director who authorized the release; and
e) the time and date of the release and a copy of the written authorization signed by the medical director.

7.2.5

A source establishment that releases a cell, tissue or organ under 7.2.1 before the donor suitability assessment is complete shall, after the release, complete the assessment and carry out any other appropriate follow-up testing and forward the results to the transplant establishment.

8. DISTRIBUTION

8.1 General

8.1.1

Each establishment that distributes cells, tissues or organs to another establishment shall provide the receiving establishment with the appropriate labelling and/or package inserts. Copies of any other information that is required to assess the suitability of the donor or the cells, tissues or organs for transplantation, except information that compromises donor confidentiality, shall be provided to the transplanting physician on request.

8.1.2

The records maintained by the distributing establishment shall include the donor identification number for cells, tissues or organs. In addition, the records should include, but not be limited to, the following:

a) the name and address of the receiving establishment;
b) the name of the establishment personnel who placed the request;

c) the name of the establishment personnel filling the request;
d) the date the request was placed and filled;
e) the type and quantity of cells, tissues or organs requested;
f) the retrieval and/or expiration dates;
g) the type and amount of refrigerant used for shipment, if applicable;
h) the date of shipment; and
i) recipient identifying information.

8.2 Importer of Cells, Tissues and Organs

8.2.1

The importer shall verify that the foreign processor of the cells, tissue or organ is in compliance with the requirements of this *Guidance Document* and applicable laws and regulations.

8.3 Transportation

8.3.1

Transportation arrangements by all establishments shipping cells, tissues or organs shall not risk the safety and integrity of the cells, tissues or organs. The shipping container shall be validated to ensure that the safety and integrity of cells, tissues and organs is maintained during transit.

8.3.2

The exterior of the shipping container should clearly display, if applicable and appropriate:
a) the name, address, donor identification number, and telephone number of the distributing and receiving establishments;
b) the type of cells, tissues, or organs;
c) the type and quantity of the refrigerant used;
d) any enclosed hazardous material;
e) recommended storage conditions; and
f) any special handling instructions.

8.4 Receiver of Cells, Tissues and Organs

8.4.1

All establishments receiving cells, tissues and organs shall be responsible for verification of shipment and for obtaining and retaining records that allow tracking of donor cells, tissues and organs to the recipient. The transplant centre shall retain all recipient information and ensure that its records link the donor to the recipient.

8.4.2

Agreements shall be in place between all cell, tissue or organ processors and distributors and the last establishment that receives the cells, tissues or organs to allow access to all information required for donor-recipient tracking (see Clause 4). These agreements shall be documented in the SOP of the processor, distributor and last establishment to receive cells, tissues or organs.

8.4.3

The receivers of cells, tissues or organs shall promptly provide information to the processors and distributors of cells, tissues or organs about complications or technical problems with the use of the cells, tissues or organs.

8.4.4

All cells, tissues and organs forwarded to another establishment by the receiver shall be accompanied by the appropriate labelling and/or package insert to facilitate tracking and suitability.

9. ADVERSE EVENT MONITORING AND RECALLS

9.1 General

All confirmed positive tests for transmissible diseases in the recipient, suspected of being attributable to cell, tissue or organ transplantation shall be reported in a timely fashion to establishments and to physicians involved in any manner with the cells, tissues or organs retrieved from the same donor and to public authorities as required by applicable laws and regulations. If the event is reported verbally, a confirmatory written notice must be sent as soon as possible. Notification shall be documented in the donor's records.

9.2 Investigation, Notification and Reporting

9.2.1

Identified transmission of disease and/or suspected serious adverse events shall be reported to federal, provincial, territorial or local health authorities as required by law.

9.2.2

Where there is evidence or reasonable grounds to believe that a transmissible agent or disease has been transmitted through the transplant, the establishment shall, without delay:

a) stop the distribution of all cells, tissues and organs in his or her possession having the same donor identification number as the cells, tissues and organs suspected of infectious transmission; and

b) provide a written report to the source establishment;
   i) advising that the cells, tissues or organs that the source establishment processed may be contaminated by a named confirmed or suspected infectious agent; and

ii) specifying the donor identification number of the suspected cells, tissues and organs.

9.2.3

Where a source establishment receives a report as described in Clause 9.2.2, or otherwise has reasonable grounds to believe that cells, tissues or organs already distributed may be contaminated by an infectious or transmissible agent or integrity may be compromised, the establishment shall, without delay:

a) identify the donor of the cells, tissues or organs and quarantine all cells, tissues or organs from the donor that are in the establishment's possession;
b) use all reasonable means to identify and locate each establishment that received cells, tissues or organs obtained from the donor;
c) give a written notice specifying the donor identification number of the cells, tissues or organs believed to be contaminated, naming the confirmed or suspected infectious or transmissible agent or the compromise of integrity, and indicating that the cells, tissues or organs shall be quarantined pending the completion of an investigation or must be destroyed. This notice shall be given to
    i) any person to whom the establishment distributed cells, tissues or organs having the donor identification number specified in the notice; and
    ii) any other person who the establishment identified as receiving cells, tissues or organs from that donor source; and
    iii) conduct an investigation to determine whether any of the cells, tissues or organs from the donor source are contaminated by an infectious or transmissible agent or compromise of integrity.

9.2.4

Every establishment shall, at the request of the source establishment conducting the investigation, provide the source establishment with any relevant information in its possession with respect to cells, tissues or organs that were distributed.

9.2.5

Where the results of the investigation demonstrate that the cells, tissues or organs are not contaminated by an infectious agent, the source establishment shall notify each person contacted about the potential infectious agent, in writing, that it is permissible to distribute the cells, tissues and organs having the donor identification number specified in the list of cells, tissues or organs that are not contaminated.

9.2.6

Where the results of the investigation demonstrate that all or some of the cells, tissues or organs are contaminated by an infectious agent, or the results are inconclusive as to whether the cells, tissues or organs are contaminated, the source establishment shall notify each person contacted about the potential infectious agent, in writing, that the cells, tissues or organs having the donor

identification number specified in the list of cells, tissues or organs that are contaminated must be collected by the source establishment or destroyed.

9.2.7

Where an establishment receives a notice from the source establishment about a potential infectious agent, the establishment shall provide a written report to the source establishment, as soon as possible, indicating for each donor identification number referred to in the notice the number of cells, tissues or organs received by the establishment and the number that was distributed or destroyed.

9.3 Recall

The SOP shall describe the procedure for recall or notification, as well as all documentation required. Documentation shall include the following:

a) reason for the recall;
b) steps taken to quarantine recalled cells, tissues or organs that have not been transplanted or the return of such cells, tissues or organs to the establishment;
c) all communications and correspondence regarding the recall;
d) final disposition of cells, tissues or organs;
e) corrective actions recommended and implemented;
f) notification of recipients; and
g) packaging and shipping instructions for consignees, if applicable.