Guidance Document for Source Establishments – Reporting Adverse Reactions to Human Cells, Tissues and Organs

(Effective Date: 2010-05-25)

Canada Vigilance Adverse Reaction Monitoring Program and Database, a program of MedEffect™ Canada

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Foreword

Guidance documents are meant to provide assistance on how to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate justification. Alternate approaches 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 a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with relevant sections of other applicable guidance documents.

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1 Introduction

1.1 Scope

This guidance document provides source establishments with assistance on how to comply with adverse reaction reporting obligations under the *Food and Drugs Act* and the *Safety of Human Cells, Tissues and Organs for Transplantation Regulations*[1] (these regulations are referred to hereafter as "the Regulations"). Error and accident reporting requirements for source establishments are also outlined in this guidance document in section 1.4.

The adverse reaction reporting requirements covered by this guidance document apply only to human organs and minimally manipulated cells and tissues intended for homologous use in transplantation in another individual.

This guidance document for the reporting of adverse reactions to human cells, tissues and organs (CTO) accompanies the Guidance Document for Cell, Tissue and Organ Establishments – Safety of Human Cells, Tissues and Organs for Transplantation[2], which provides general guidance on all aspects of the Regulations[1] to establishments that process, distribute, import or transplant CTO for homologous use in transplantation in another individual.

Other agencies, branches and/or directorates of Health Canada and certain Health Canada partners collect adverse reaction reports on other products. Appendix 4 provides further details on these other reporting programs.

1.2 Definitions

Definitions for a number of terms used in this document are set out below. A complete glossary is included in Appendix 1.

"Adverse reaction" as defined in the Regulations[1] means an undesirable response in the recipient to transplanted cells, tissues or organs, including the transmission of a disease or disease agent.

"Cell" as defined in the Regulations[1] means the fundamental biological unit of a human organism that is for use in transplantation.

"Establishment" as defined in the Regulations[1] means 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:

(*a*) importation;
(*b*) processing;
(*c*) distribution; and
(*d*) transplantation.

"Homologous" as defined in the Regulations[1] in respect of a cell, tissue or organ, means that the cell, tissue or organ performs the same basic function after transplantation.

"Minimally manipulated" as defined in the Regulations[1] means

(*a*) 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
(*b*) in respect of cells and non-structural tissue, that the processing does not alter the biological characteristics that are relevant to their claimed utility.

"Organ" as defined in the Regulations[1] means a perfusable human organ for use in transplantation, whether whole or in parts, and whose specific function is intended to return after revascularization and reperfusion. It includes any adjunct vessels that are retrieved with the organ for use in organ transplantation.

"Processing" as defined in the Regulations[1] means, in respect of CTO, any of the following activities:

(a) donor screening;
(b) donor testing;
(c) donor suitability assessment;
(d) retrieval, except for organs and islet cells;
(e) testing and measurements performed on the CTO after they are retrieved;
(f) preparation for use in transplantation, except for organs;
(g) preservation;
(h) quarantine;
(i) banking; and
(j) packaging and labelling.

"Serious adverse reaction" as defined in the Regulations[1] means an adverse reaction that results in any of the following consequences for the recipient:

(*a*) their in-patient hospitalization or its prolongation;
(*b*) persistent or significant disability or incapacity;
(*c*) medical, dental or surgical intervention to preclude a persistent or significant disability or incapacity;
(*d*) a life-threatening condition; and
(*e*) death.

"Source establishment" as defined in the Regulations[1] means

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

"Tissue" as defined in the Regulations[1] means a functional group of human cells for use in transplantation. It includes the cells and tissues listed in the definition "tissue" in section 3.1 of the general standard (see Appendix 1 for the definition of General Standard) except for paragraphs *(g)* and *(l)*.

1.3 Adverse Reaction Reporting for Human Cells, Tissues and Organs

Pursuant to section 51(1)(b) of the Regulations[1], unexpected serious adverse reactions that are thought to involve the transmission of an infectious disease or disease agent must be reported to the **Marketed Health Products Directorate (MHPD)** of Health Canada by source establishments.

For the definitions of "adverse reaction" and "serious adverse reaction", refer to section 1.2 of this guidance document.

An unexpected adverse reaction following the transplantation of a CTO includes the unintended and unforeseen transmission of an infectious disease or disease agent, for example any bacterial, viral or fungal infection that is caused by a contaminated transplanted CTO. The laboratory identification of the implicated infectious disease agent does not need to have been confirmed in order to proceed with reporting if there is sufficient clinical evidence to suspect infectious disease transmission. It does not include the transmission of an infectious disease or disease agent where such transmission is expected.

For example, transmission of hepatitis C virus (HCV) from an HCV positive donor to an HCV negative recipient would not be an unexpected adverse reaction, as this would be an expected outcome resulting from the use of an HCV positive organ. In the case where the recipient develops HCV following transplantation of an organ that was not known to be HCV positive, such an outcome would be considered an unexpected adverse reaction.

In the case of organ transplantation where recipients are immunosuppressed, clinical presentation of infectious diseases may be atypical. In addition, transplantation as a mode of transmission of an infectious disease should not be ruled out, even if not documented in the literature, especially in the case of rare infectious diseases, as was demonstrated in the case of rabies in 2004[3,4].

All establishments are also required to notify other relevant establishments of unexpected adverse reactions in accordance with sections 47 to 49 of the Regulations[1].

1.4 Reporting of Errors or Accidents

Pursuant to section 51(1)(a) of the Regulations[1], suspected errors and accidents that are identified after the distribution of CTO and that could lead to a serious adverse reaction involving the transmission of an infectious disease or disease agent must be reported by source establishments to Health Canada's **Health Products and Food Inspectorate**. Further information is available in the Guidance Document for Cell, Tissue and Organ Establishments – Safety of Human Cells, Tissues and Organs for Transplantation[2].

An error, as defined in the Regulations[1], means 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. An accident, as defined in the Regulations[1], means an unexpected event that is not attributable to a deviation from the standard operating procedures or applicable laws and that could adversely affect the safety of a transplant recipient or the safety, efficacy or quality of cells, tissues or organs.

All establishments are also required to notify other relevant establishments of errors or accidents in accordance with sections 43 to 46 of the Regulations[1].

1.5 Cells, Tissues and Organs Regulations

The sections of the applicable Regulations[1] that set out the adverse reaction reporting requirements for CTO are listed below.

1.5.1 Application (Sections 2, 3)

Scope of the Regulations[1]
2. These Regulations apply only to organs and minimally manipulated cells and tissues.

Non-application - various therapeutic products
3. (1) These 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 except for 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 primary function;
(e) medical devices that contain cells or tissues and that 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; and
(j) semen that is regulated under the *Processing and Distribution of Semen for Assisted Conception Regulations*.

1.5.2 Adverse Reactions (Sections 47-54, 59(h), 62(2))

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; and
(c) notify the following establishments:
(i) the relevant source establishment, and
(ii) if the cells, tissues or organs were imported, the establishment that imported them.

Exception – 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; and
(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.

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, and

(iv) any establishment to which it distributed implicated cells, tissues or organs; and

(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; and

(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.

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; and

(b) forward a copy of the notice to every establishment to which it distributed implicated cells, tissues or organs.

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.

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; and

(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; and

(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.

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.

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.

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; and
(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.

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:

(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.

Retention – 10 years after record creation
62. (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); and
(b) reports of audits conducted under section 76, if applicable.

2 General Procedures for Adverse Reaction Reporting

2.1 Adverse Reaction Reporting

In accordance with sections 51 and 54 of the Regulations[1], source establishments conducting an investigation into an adverse reaction involving CTO for whose processing they are responsible, must submit to MHPD the following reports of unexpected serious adverse reactions that are thought to involve the transmission of an infectious disease or disease agent:

a) a preliminary report within 24 hours of the start of an investigation;
b) an update report within 15 days after the start of an investigation and every 15 days after that; and
c) a final report on completion of the investigation.

The preferred adverse reaction reporting format for source establishments is the:

- Mandatory Adverse Reaction Reporting Form for Industry (see section 3 of this guidance document)

Source establishments should assign a unique report number for each adverse reaction case reported to them.

2.1.1 Preliminary Report (Initial Report)

Pursuant to section 51(2)(a) of the Regulations[1], within 24 hours of the start of an investigation, the source establishment must report to MHPD all available information regarding the unexpected serious adverse reaction that is thought to involve the transmission of an infectious disease or disease agent. The information provided in this report could include, but is not limited to, the name of the suspected infectious disease and/or disease agent, the description of the CTO, the number of recipients potentially affected, and the identification code of the donor(s) (if known).

The source establishment should send to MHPD one reporting form for each recipient affected by the adverse reaction. Refer to section 3 of this guidance document for more information.

2.1.2 Update Reports (Follow-up Reports)

As required by section 51(2)(b) of the Regulations[1], within 15 days after the start of the investigation and every 15 days after that until the final report is submitted, the source establishment must provide MHPD with an update on any new information about the unexpected serious adverse reaction, the progress made in the investigation during those 15 days, and the steps taken to mitigate further risks. This update should also include both clinical information (e.g., progress of patient, outcome of infection, if known, results of clinical investigation) as well as information regarding the identification of the root cause of the infection (e.g., source of contamination, how contamination was ruled out, actions taken).

2.1.3 Final Report

On completion of the investigation, the source establishment must submit a final report to MHPD, as per section 54 of the Regulations[1]. The final report provided is to be detailed and is to indicate the results of the investigation; it should include conclusions, specify any infectious agent(s), results of any tests performed, follow-up and corrective actions taken, and details of the reconciliation of the CTO and their final disposition (number processed, distributed, transplanted, quarantined, destroyed).

2.2 Notification, Action and Quarantine by Establishments

The adverse reaction reporting requirements set out under section 51(1)(b) of the Regulations[1] are connected to a series of risk mitigation steps that a source establishment is required to perform under section 48 of the Regulations[1], when an adverse reaction is suspected to have occurred in relation to CTO for whose processing the source establishment is responsible. The Regulations[1] require that the source establishment that discovers or suspects that an unexpected adverse reaction has occurred, must take steps as outlined in section 48 of the Regulations[1] as follows:

2.2.1 Quarantine by Source Establishment

In accordance with section 48(1)(a) of the Regulations[1], all implicated CTO that a source establishment is responsible for processing must be quarantined. Quarantine will usually involve at least all CTO originating from the same donor. However, should the investigation uncover other potential causative factors, the quarantine may apply to other CTO as well.

2.2.2 Notice from Source Establishment

In accordance with section 48(1)(b) of the Regulations[1], the source establishment is also required to send a notice, as described in 48(2) of the Regulations[1] (see also section 2.2.2.1 of this guidance document), to:

a) the establishment that imported the CTO, if applicable;

b) any source establishment from which it received a donor referral, if applicable. For example, a tissue bank shall inform the Organ Donation Organization (ODO, another source establishment) if the donor was referred to it by the ODO;

c) any source establishment to which it made a donor referral. For example, if an ODO is made aware of an unexpected adverse reaction after transplantation, it shall inform any source establishments, such as tissue banks, to which it referred the donor, as the tissues may be carrying the same infectious disease agent; and

d) any establishment to which it distributed implicated CTO.

2.2.2.1 Contents of the Notice

In accordance with section 48(2) of the Regulations[1], the notice must include:

a) a description of the nature of the adverse reaction. Useful information may include a description of the signs and symptoms, temporal relationship with the transplantation, relevant laboratory test results;

b) an explanation of how the safety of the implicated CTO may have been compromised, if known;

c) the donor identification codes of all implicated CTO. This is important in order for establishments to know which CTO need to be quarantined;

d) the name of any suspected transmissible disease or disease agent, if known. If the disease or disease agent has not been identified, it would be useful to know the diseases/agents that are suspected and/or any preliminary results (Gram stain, etc.); and

e) a statement requiring all implicated CTO to be quarantined immediately and until further notice from the source establishment, and specifying any other corrective action that must be taken.

2.2.3 Action on Receipt of Notice by Establishments

Pursuant to section 49 of the Regulations[1], an establishment that is not a source establishment and that receives a notice or a copy of such a notice under section 48 of the Regulations[1] must immediately:

a) quarantine all implicated CTO (all CTO for which identification codes were specified in the notice) in its possession; and

b) forward a copy of the notice to every establishment to which it distributed implicated CTO. This notice helps ensure that the requirement to quarantine all CTO that may have been compromised, is transmitted all the way down the distribution chain. It is important that all establishments in possession of implicated CTO be informed of the need to quarantine. As a source establishment may not be aware if CTO had been further distributed after delivering them to an establishment, it becomes every establishment's responsibility to forward the notice to whomever they may have sent the CTO.

2.2.4 Investigation by Source Establishment

In addition, in accordance with section 48(1)(c) of the Regulations[1], the source establishment that discovers or suspects that an unexpected adverse reaction has been associated with a CTO must initiate an investigation into the adverse reaction. Section 51 of the Regulations[1] further describes the investigation.

2.3 Records

In accordance with sections 55 to 63 of the Regulations[1], all source establishments must keep records with respect to CTO for whose processing they are responsible. A source establishment must maintain in these records documentation of any adverse reactions and their investigation and of any corrective action taken, for 10 years after the date of their creation (see sections 59(h) and 60(f)).

3 Completing the Mandatory Adverse Reaction Reporting Form for Industry

Source establishments should submit the completed Mandatory Adverse Reaction Reporting Form for Industry by facsimile to the Canada Vigilance national office at 613-957-0335 (see Appendix 3 of this guidance document). The Mandatory Adverse Reaction Reporting Form for Industry is available on the Health Canada Web site at:
http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/ar-ei_indus_form-eng.php

The Mandatory Adverse Reaction Reporting Form for Industry contains specific instructions on how to complete the reporting form. Those instructions should be followed to avoid delays in the processing of the adverse reaction report.

In addition to the instructions provided on the reporting form itself, the following general guidance is also provided for source establishments when preparing an adverse reaction report for submission to MHPD.

a) The Mandatory Adverse Reaction Reporting Form for Industry should be used for the preliminary report (initial), the update report(s) (follow-up), and the final report for submission to MHPD. One reporting form per affected recipient should be provided to MHPD.

b) The update and final reports should consist of an updated Mandatory Adverse Reaction Reporting Form for Industry as well as the investigation document. All updated information on the reporting form and on the investigation document should be clearly marked. The steps taken as part of the investigation should be presented in chronological order in the investigation document.

c) Mandatory Adverse Reaction Reporting Form for Industry – **Box A5** (Source Establishment Report No.): If the reported case is part of a cluster, this should be indicated on the reporting form and cross-referenced to other report numbers where possible. As mentioned above, one reporting form for each affected recipient should be provided to MHPD. Each affected recipient should be represented by a unique Source Establishment Report Number.

d) Mandatory Adverse Reaction Reporting Form for Industry – **Boxes C6 to C8** (Adverse Reaction): Provide all relevant information on the adverse reaction. Such information may include donor screening tests, pre- and post- processing culture results, laboratory or other clinical investigation results, a description of the clinical pictures and the temporal relationship with the transplantation, signs and symptoms, presence of concomitant medications or medical conditions, etc. Also include the name of any suspected transmissible disease or disease agent, if known. If the disease or disease agent has not been identified, it would be useful to know the diseases/agents that are suspected and/or any preliminary results (Gram stain, clinical symptoms, etc.).

e) Mandatory Adverse Reaction Reporting Form for Industry – **Section D** (Health Products): In some circumstances, more than one product may be suspected as the cause of the infection (e.g., more than one CTO, concomitant blood transfusion or immunosuppressant). These should also be identified as suspected products on the same form.

f) Additional pages may be attached to the Mandatory Adverse Reaction Reporting Form for Industry if more space is needed.

Appendix 1 Glossary: Definitions and Terminology

Accident[1]
Accident means an unexpected event that is not attributable to a deviation from the standard operating procedures or applicable laws and that could adversely affect the safety of a transplant recipient or the safety, efficacy or quality of cells, tissues or organs.

Adverse Reaction[1]
Adverse reaction means an undesirable response in the recipient to transplanted cells, tissues or organs, including the transmission of a disease or disease agent.

Canada Vigilance Adverse Reaction Monitoring Program
Health Canada's Canada Vigilance Adverse Reaction Monitoring Program is responsible for the collection and assessment of adverse reaction reports related to the following marketed health products: pharmaceuticals, biologics (including fractionated blood products, as well as therapeutic and diagnostic vaccines), natural health products, radiopharmaceuticals and cells, tissues and organs. Canada Vigilance is a program of MedEffect™ Canada and is operated by the Marketed Health Products Directorate.

Cell[1]
Cell means the fundamental biological unit of a human organism that is for use in transplantation.

Donor[1]
Donor means a living or deceased person from whom cells, tissues or organs are retrieved.

Donor Identification Code[1]
Donor identification code means the unique numeric or alphanumeric designation that is assigned by the source establishment to a donor under section 56 and that associates each cell, tissue and organ, or part of one, to that donor.

Donor Screening[1]
Donor screening means 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.

Error[1]
Error means 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[1]
Establishment means 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:

(*a*) importation;
(*b*) processing;
(*c*) distribution; and
(*d*) transplantation.

General Standard[1]
General standard means National Standard of Canada CAN/CSA-Z900.1 entitled *Cells, Tissues, and Organs for Transplantation and Assisted Reproduction: General Requirements*, as amended from time to time.

Homologous[1]

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

MedEffect™ Canada

MedEffect™ Canada has been developed by Health Canada's Marketed Health Products Directorate:

a) to provide centralized access to relevant and reliable health product safety information as it becomes available, in an easy to find, easy to remember location. This includes access to Health Canada's advisories, warnings and recalls; the Canadian Adverse Reaction Newsletter (CARN); and the Canada Vigilance Adverse Reaction Online Database;

b) to make it as simple and efficient as possible for health professionals and consumers to complete and file adverse reaction reports via Web, phone, fax or mail; and

c) to build awareness about the importance of reporting adverse reactions to Health Canada, and how this information is used to identify and communicate potential risks.

Minimally Manipulated[1]

Minimally manipulated means

(*a*) 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

(*b*) in respect of cells and non-structural tissue, that the processing that does not alter the biological characteristics that are relevant to their claimed utility.

Organ[1]

Organ means a perfusable human organ for use in transplantation, whether whole or in parts, and whose specific function is intended to return after revascularization and reperfusion. It includes any adjunct vessels that are retrieved with the organ for use in organ transplantation.

Package Insert[1]

Package insert means the document that is prepared by the source establishment to accompany a cell, tissue or organ.

Processing[1]

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, except for organs and islet cells;
(*e*) testing and measurements performed on the cells, tissues or organs after they are retrieved;
(*f*) preparation for use in transplantation, except for organs;
(*g*) preservation;
(*h*) quarantine;
(*i*) banking; and
(*j*) packaging and labelling.

Serious Adverse Reaction[1]

Serious adverse reaction means an adverse reaction that results in any of the following consequences for the recipient:

(*a*) their in-patient hospitalization or its prolongation;
(*b*) persistent or significant disability or incapacity;
(*c*) medical, dental or surgical intervention to preclude a persistent or significant disability or incapacity;

(*d*) a life-threatening condition; and

(*e*) death.

Source Establishment[1]

Source establishment means

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

(b) in the case of adjunct vessels that are retrieved with an organ and not used immediately in the organ transplantation, the relevant tissue bank;

(*c*) in the case of an organ from a living donor or lymphohematopoietic cells that are not banked, the relevant transplant establishment;

(*d*) in the case of tissues or banked lymphohematopoietic cells, the relevant cell or tissue bank; and

(e) in the case of islet cells, the establishment that prepares the cells for use in transplantation.

Standard Operating Procedures[1]

Standard operating procedures mean 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[1]

Tissue means a functional group of human cells for use in transplantation. It includes the cells and tissues listed in the definition "tissue" in section 3.1 of the general standard, except for paragraphs *(g)* and *(l)*.

Transplant[1]

Transplant means to implant cells, tissues or organs into a recipient.

Appendix 2 References

[1]*Safety of Human Cells, Tissues and Organs for Transplantation Regulations*, SOR/2007-118.

[2]Health Canada, Guidance Document for Cell, Tissue and Organ Establishments – Safety of Human Cells, Tissues and Organs for Transplantation, (2009). Available on the Health Canada Web site at: http://www.hc-sc.gc.ca/dhp-mps/brgtherap/reg-init/cell/cto_gd_ld-eng.php

[3]CDC. Investigation of Rabies Infections in Organ Donor and Transplant Recipients — Alabama, Arkansas, Oklahoma, and Texas, 2004. *MMWR*. 2004;53:586–589.

[4]Srinivasan A, Burton EC, Kuehnert MJ et al. Transmission of Rabies Virus from an Organ Donor to Four Transplant Recipients. *N Engl J Med*. 2005;352:1103-1111.

Appendix 3 Contact Information

The preferred method of reporting adverse reactions related to CTO by source establishments is by **fax**. All adverse reaction reports should be sent to:

Canada Vigilance Program
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture
Postal Locator: 0701E
Ottawa, Ontario
K1A 0K9

Telephone: 613-957-0337
Facsimile: 613-957-0335
E-mail: CanadaVigilance@hc-sc.gc.ca (DO NOT SEND REPORTS VIA E-MAIL)

Access to Information

For copies of adverse reaction reports, consult the Access to Information Web site at http://www.tbs-sct.gc.ca/gos-sog/atip-aiprp/index_e.asp

Appendix 4 Adverse Reaction Reporting Programs

Health Canada and its partners collect adverse reaction reports in order to monitor health and safety risks related to the sale and use of a variety of products. In order to avoid delays in reporting, it is important to direct adverse reaction reports to the appropriate program area of expertise. Refer to the Web site and table below, which provide further information on adverse reaction reporting specific to other products that are not within the scope of this guidance document. All adverse reaction reports related to CTO should be sent to the Canada Vigilance national office (see Appendix 3 of this guidance document).

Adverse Reaction Reporting for Specific Products:
http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/reaction-eng.php

Table 1: Adverse Reaction Reporting Programs

Products	**Program Leads**
Blood and Blood Components	Biologics and Genetic Therapies Directorate of the Health Products and Food Branch
Clinical Trial Biologics and Radiopharmaceuticals	Biologics and Genetic Therapies Directorate of the Health Products and Food Branch
Clinical Trial Natural Health Products	Natural Health Products Directorate of the Health Products and Food Branch
Clinical Trial Pharmaceutical Drugs	Therapeutic Products Directorate of the Health Products and Food Branch
Consumer Products	Consumer Product Safety Bureau of the Healthy Environments and Consumer Safety Branch
Cosmetics	Cosmetics Program of the Healthy Environments and Consumer Safety Branch
Drugs and Natural Health Products used in Animals	Veterinary Drugs Directorate of the Health Products and Food Branch
Food	Office of Food Safety and Recall of the Canadian Food Inspection Agency
Marketed Health Products: prescription and non-prescription pharmaceuticals, biologics (which include biotechnology products, recombinant and fractionated blood products, as well as therapeutic and diagnostic vaccines), natural health products, and radiopharmaceuticals	Canada Vigilance Adverse Reaction Monitoring Program of the Health Products and Food Branch
Medical Devices	Health Products and Food Inspectorate
Pesticides	Pest Management Regulatory Agency
Preventative Immunization Vaccines in Humans	Canadian Adverse Events Following Immunization Surveillance System of the Public Health Agency of Canada
Radiation-Emitting Devices	Consumer and Clinical Radiation Protection Bureau of the Healthy Environments and Consumer Safety Branch
Special Access Programme Drugs	Special Access Programme – Therapeutic Products Directorate of the Health Products and Food Branch
Veterinary Biologics	Veterinary Biologics Section of the Canadian Food Inspection Agency