

Her Excellency the Governor General in Council, on the recommendation of the Minister of Health, pursuant to section 30 of the *Food and Drugs Act*, hereby makes the annexed *Safety of Human Cells, Tissues and Organs for Transplantation Regulations*.

°S.. 2004, c. 23, s. 2

SAFETY OF HUMAN CELLS, TISSUES AND ORGANS FOR TRANSPLANTATION REGULATIONS

INTERPRETATION

Definitions

1. The following definitions apply in these Regulations.

“accident”

« *accident* »

“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.

“Act”

« *Loi* »

“Act” means the *Food and Drugs Act*.

“adverse reaction”

« *effet indésirable* »

“adverse reaction” means an undesirable response in the recipient to transplanted cells, tissues or organs, including the transmission of a disease or disease agent.

“banked”

« *mise en banque* »

“banked”, with respect to cells and tissues, means processed cells and tissues that have been determined safe for transplantation and that are stored by the source establishment in its inventory and available for distribution or transplantation.

“cell”

« *cellule* »

“cell” means the fundamental biological unit of a human organism that is for use in transplantation.

“distribute”

« *distribution* »

“distribute” does not include to transplant.

“donor”

« *donneur* »

“donor” means a living or deceased person from whom cells, tissues or organs are retrieved.

“donor assessment record”

« dossier de l'évaluation du donneur »

“donor assessment record” includes the donor screening, any available donor testing results, information obtained from the donor’s medical records and a copy of the donor consent.

“donor identification code”

« code d'identification du donneur »

“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”

« évaluation préliminaire du donneur »

“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.

“donor suitability assessment”

« évaluation de l'admissibilité du donneur »

“donor suitability assessment” means an evaluation based on the donor screening and

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

“donor testing”

« examen du donneur »

“donor testing” means the laboratory tests and measurements done on a donor or donor specimen to determine all of the following:

- (a) whether the donor has or ever had a transmissible disease or is or ever was infected with a transmissible disease agent;
- (b) donor compatibility; and
- (c) the degree of functionality of the cell, tissue or organ that is to be retrieved.

“error”

« manquement »

“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”

« établissement »

“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.

“exceptional distribution”

« distribution exceptionnelle »

“exceptional distribution” means the distribution under sections 40 to 42 of cells, tissues or organs that have not been processed under these Regulations.

“exterior label”

« étiquette extérieure »

“exterior label” means the label that is affixed to the exterior package.

“exterior package”

« emballage extérieur »

“exterior package” means the outermost package in which a cell, tissue or organ is delivered, transported or shipped.

“general standard”

« norme générale »

“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”

« homologue »

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

“interior label”

« étiquette intérieure »

“interior label” means the label that is affixed to the interior package.

“interior package”

« emballage intérieur »

“interior package” means the innermost package of a cell, tissue or organ that has a non-sterile exterior.

“lymphohematopoietic standard”

« norme sur les cellules lymphohématopoïétiques »

“lymphohematopoietic standard” means National Standard of Canada CAN/CSA-Z900.2.5 entitled *Lymphohematopoietic Cells for Transplantation*, as amended from time to time.

“medical director”

« directeur médical »

“medical director”, in respect of an establishment, means a physician or dentist who is licensed under the laws of the jurisdiction in which the establishment is situated to provide health care or dental care and who is responsible for the application of the standard operating procedures and for all medical or dental procedures carried out there, as the case may be.

“minimally manipulated”

« manipulation minimale »

“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 nonstructural tissue, that the processing does not alter the biological characteristics that are relevant to their claimed utility.

“ocular standard”

« norme sur les tissus oculaires »

“ocular standard” means National Standard of Canada CAN/CSA-Z900.2.4 entitled *Ocular Tissues for Transplantation*, as amended from time to time.

“organ”

« *organe* »

“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.

“organ standard”

« *norme sur les organes* »

“organ standard” means National Standard of Canada CAN/CSAZ900-Z900.2.3 entitled *Perfusable Organs for Transplantation*, as amended from time to time.

“package insert”

« *encart informatif* »

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

“processing”

« *traitement* »

“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.

“quality assurance system”

« *système d'assurance de la qualité* »

“quality assurance system” means the co-ordinated activities of an establishment that relate to the safety of cells, tissues and organs. It includes

- (a) the standard operating procedures;
- (b) records to demonstrate that the standard operating procedures have been implemented; and
- (c) audit processes to verify that the standard operating procedures are being implemented.

“scientific director”

« *directeur scientifique* »

“scientific director”, in respect of an establishment, means an individual who is responsible for the application of the standard operating procedures and for all technical procedures carried out there.

“serious adverse reaction”

« *effet indésirable grave* »

“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”

« *établissement central* »

“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”

« *procédures d'opération normalisées* »

“standard operating procedures” means 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”

« *tissu* »

“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).

“tissue standard”

« *norme sur les tissus* »

“tissue standard” means National Standard of Canada CAN/CSA-Z900.2.2 entitled *Tissues for Transplantation*, as amended from time to time.

“transplant”

« *transplantation* »

“transplant” means to implant cells, tissues or organs into a recipient.

APPLICATION

Scope of Regulations

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*.

Non-application — regulations

(2) No other regulation made under the Act applies to cells, tissues or organs that are the subject of these Regulations.

PROHIBITION

Transplantation

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

Importation — cells and tissue

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

Importation — organs and lymphohematopoietic cells

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

REGISTRATION

Requirement to register

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

Exception

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

Application

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

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

Information on request

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

Registration number

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

Validity

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

Refusal

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

When registration may be cancelled

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

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

Actions before cancellation

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

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

Notice of cancellation

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

Action by establishment when registration cancelled

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

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

Cancellation in urgent circumstances

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

Request to reconsider

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

Opportunity to be heard

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

Ongoing requirement to notify Minister

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

Cessation of activity

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

Contents of notice

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

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

Additional information

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

SOURCE ESTABLISHMENT

Responsibility

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

establishment, and for determining whether the cells, tissues and organs are safe for transplantation.

PROCESSING

GENERAL

Documented evidence

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

When pooling permitted

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

DONOR SUITABILITY ASSESSMENT

Requirements — cell, tissue and organ donors

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

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

Plasma dilution algorithm

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

Additional exclusion criteria — tissue donors

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

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

Additional exclusion criteria — ocular tissue donors

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

Additional requirements — organ and islet cell donors

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

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

Exception — imported organs

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

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

Requirements — lymphohematopoietic cells

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

- (a) obtain the donor information and history in accordance with sections 12.2.2.2 and 12.2.2.3 of the lymphohematopoietic standard;
- (b) perform a physical examination of the donor in accordance with section 13.2 of the lymphohematopoietic standard;
- (c) determine that the donor is not unsuitable to donate on the basis of the contraindications or exclusion criteria set out in section 13.1.3 of the lymphohematopoietic standard;
- (d) perform the tests specified in section 12.2.2.4 of the lymphohematopoietic standard; and
- (e) perform appropriate and effective tests for the diseases or disease agents specified in section 14.2.3 of the lymphohematopoietic standard.

Exception — imported lymphohematopoietic cells

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

- (a) have documentation of the donor suitability assessment;
- (b) perform the tests specified in section 12.2.2.4 of the lymphohematopoietic standard;
- (c) perform appropriate and effective tests for the diseases or disease agents specified in section 14.2.3 of the lymphohematopoietic standard; and

(d) determine that the donor is not unsuitable to donate on the basis of the exclusion criteria set out in section 13.1.3.4 of the lymphohematopoietic standard.

RETRIEVAL

Retrieval interval — tissues

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

TESTING

Licensed diagnostic devices

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

(a) in Canada, if the testing is performed in Canada; or

(b) in Canada or the United States, if the testing is performed outside Canada.

Exception — lymphohematopoietic cells

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

In vitro diagnostic devices — cells and tissues

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

Exception — syphilis

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

Bacteriological testing — tissues

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

PACKAGING AND LABELLING

Packaging

Packaging materials

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

Labelling

Language requirement

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

Cells, except islet cells

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

TABLE TO SUBSECTION 30(1)
 LABELLING REQUIREMENTS FOR CELLS, EXCEPT ISLET CELLS

Item	Column 1 Required information	Column 2 From retrieval establishment to transplant establishment			Column 3 From retrieval establishment to cell bank			Column 4 From cell bank to any other establishment		
		Interior label	Package insert	Exterior label	Interior label	Package insert	Exterior label	Interior label	Package insert	Exterior label
Information about donor and cell										
1.	Name of cell	X	X		X	X		X	X	
2.	Description of cell		X			X			X	
3.	Donor identification code, clearly labelled as such	X	X					X	X	
4.	Information capable of identifying the donor				X	X				
5.	Donor assessment record					X				
6.	ABO group and Rh factor of donor, if applicable	X	X		X	X		X	X	
7.	The hazard symbol entitled “Biohazardous Infectious Material” set out in Schedule II to the <i>Controlled Products Regulations</i> , if applicable	X		X	X		X	X		X
Retrieval information										
8.	Date, time and time zone of retrieval		X			X				
9.	Information specific to retrieval procedure		X			X				
Processing information										
10.	Name of anticoagulant and other additive, if applicable		X			X			X	
11.	Statement “For Autologous Use Only”, if applicable	X	X		X	X		X	X	
Information for transplant establishment										
12.	Statement that the cell has been declared safe for transplantation								X	
13.	Statement “For Exceptional Distribution”, if applicable		X						X	
14.	If applicable, the reasons for exceptional distribution and a statement of how the cell does not meet the		X						X	

Item	Column 1 Required information	Column 2 From retrieval establishment to transplant establishment			Column 3 From retrieval establishment to cell bank			Column 4 From cell bank to any other establishment		
		Interior label	Package insert	Exterior label	Interior label	Package insert	Exterior label	Interior label	Package insert	Exterior label
	requirements of these Regulations									
15.	Instructions on how to report errors, accidents and adverse reactions								X	
16.	Expiry date and time, if applicable							X	X	
Establishment information										
17.	Name of retrieval establishment, its civic address and contact information		X	X		X	X			
18.	Name of source establishment, its civic address and contact information		X	X		X	X		X	X
19.	Registration number of source establishment, clearly labelled as such		X	X					X	X
20.	Name of transplant establishment, if known, its civic address and contact information			X						X
Storage information										
21.	Statement "Human cells for transplant"			X		X				X
22.	Handling instructions for storage and for storage during transportation			X		X				X

Pancreas and islet cells

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

TABLE TO SUBSECTION 30(2)
LABELLING REQUIREMENTS FOR PANCREAS AND ISLET CELLS

Item	Column 1 Required information	Column 2 PANCREAS: From retrieval establishment to source establishment			Column 3 ISLET CELLS: From source establishment to any other establishment		
		Interior label	Package insert	Exterior label	Interior label	Package insert	Exterior label
Information about donor and organ or islet cells							
1.	Name of organ or cells, as applicable	X	X		X	X	
2.	Description of organ or cells, as applicable		X			X	
3.	Donor identification code, clearly labelled as such				X	X	
4.	Information capable of identifying the donor	X	X				
5.	Donor assessment record		X				
6.	ABO group and Rh factor of donor, if	X	X		X	X	

Item	Column 1 Required information	Column 2 PANCREAS: From retrieval establishment to source establishment			Column 3 ISLET CELLS: From source establishment to any other establishment		
		Interior label	Package insert	Exterior label	Interior label	Package insert	Exterior label
	applicable						
7.	The hazard symbol entitled "Biohazardous Infectious Material" set out in Schedule II to the <i>Controlled Products Regulations</i> , if applicable	X		X	X		X
Retrieval information							
8.	Date, time and time zone of asystole or aortic clamping, if applicable		X				
9.	Date, time and time zone of retrieval		X				
10.	Information specific to retrieval procedure		X				
11.	Name of perfusion solution		X				
Processing information							
12.	Name of storage solution		X				
13.	Name of additives, if applicable					X	
Information for establishments							
14.	Statement that the cells have been declared safe for transplantation					X	
15.	Statement "For Exceptional Distribution", if applicable		X		X	X	
16.	If applicable, the reasons for exceptional distribution and a statement of how the organ or cells do not meet the requirements of these Regulations		X			X	
17.	Instructions on how to report errors, accidents and adverse reactions		X			X	
18.	Expiry date and time, if applicable				X	X	
Establishment information							
19.	Name of retrieval establishment, its civic address and contact information		X	X		X	X
20.	Name of source establishment, its civic address and contact information		X	X		X	X
21.	Registration number of source establishment, clearly labelled as such		X	X		X	X
22.	Name of other establishment, its civic address and contact information						X
Storage information							
23.	Statement "Human organ for transplant" or "Human cells for transplant", as applicable			X			X
24.	Handling instructions for storage and for storage during transportation			X			X

Tissues

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

TABLE TO SECTION 31
LABELLING REQUIREMENTS FOR TISSUE

Item	Column 1 Required information	Column 2 From retrieval establishment to tissue bank			Column 3 From tissue bank to any other establishment		
		Interior label	Package insert	Exterior label	Interior label	Package insert	Exterior label

Information about donor and tissue							
1.	Name of tissue, and whether left or right side, if applicable	X	X		X	X	
2.	Description of tissue		X			X	
3.	Donor identification code, clearly labelled as such				X	X	
4.	Information capable of identifying the donor	X	X				
5.	Donor assessment record		X				
6.	The hazard symbol entitled "Biohazardous Infectious Material" set out in Schedule II to the <i>Controlled Products Regulations</i> , if applicable	X		X	X		X
Retrieval information							
7.	Date, time and time zone of asystole or aortic clamping, if applicable		X				
8.	Date, time and time zone of retrieval		X				
9.	Information specific to retrieval procedure		X				
Processing information							
10.	Name of storage solution, if applicable		X			X	
11.	Name of anticoagulant and other additive, if applicable					X	
12.	Statement that the tissue has been irradiated, if applicable				X	X	
13.	Description of the disinfection and sterilization processes that were used, if applicable					X	
14.	Statement "For Autologous Use Only", if applicable	X	X		X	X	
Information for transplant establishment							
15.	Tissue-specific instructions for preparation for use, if applicable					X	
16.	Statement that the tissue has been declared safe for transplantation					X	
17.	Statement "For Exceptional Distribution", if applicable				X	X	
18.	If applicable, the reasons for exceptional distribution and a statement of how the tissue does not meet the requirements of these Regulations					X	
19.	Instructions on how to report errors, accidents and adverse reactions					X	
20.	Expiry date and time, if applicable				X	X	
Establishment information							
21.	Name of retrieval establishment, its civic address and contact information		X	X			
22.	Name of source establishment, its civic address and contact information		X	X		X	X
23.	Registration number of source establishment, clearly labelled as such					X	X
24.	Name of transplant establishment, if known, its civic address and contact information						X
Storage information							
25.	Statement "Human tissue for transplant"			X			X
26.	Handling instructions for storage and for storage during transportation			X			X

Organs

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

TABLE TO SECTION 32
LABELLING REQUIREMENTS FOR ORGANS

Item	Column 1 Required information	Column 2 DECEASED DONOR: From retrieval establishment to transplant establishment			Column 3 LIVING DONOR: From retrieval establishment to transplant establishment		
		Interior label	Package insert	Exterior label	Interior label	Package insert	Exterior label
Information about donor and organ							
1.	Name of organ, and whether left or right side, if applicable	X	X	X	X	X	
2.	Description of organ		X			X	
3.	Donor identification code, clearly labelled as such	X	X		X	X	
4.	All information in the donor assessment record that is not capable of identifying the donor		X				
5.	ABO group and Rh factor of donor	X	X		X	X	
6.	The hazard symbol entitled "Biohazardous Infectious Material" set out in Schedule II to the <i>Controlled Products Regulations</i> , if applicable	X		X	X		X
Retrieval information							
7.	Date, time and time zone of asystole or aortic clamping, if applicable		X				
8.	Date, time and time zone of retrieval		X			X	
9.	Information specific to retrieval procedure		X			X	
10.	Name of perfusion solution		X			X	
Processing information							
11.	Name of storage solution		X			X	
Information for transplant establishment							
12.	Statement that the organ has been declared safe for transplantation		X				
13.	Statement "For Exceptional Distribution", if applicable	X	X		X	X	
14.	If applicable, the reasons for exceptional distribution and a statement of how the organ does not meet the requirements of these Regulations		X			X	
15.	Instructions on how to report errors, accidents and adverse reactions		X			X	
Establishment information							
16.	Name of retrieval establishment, its civic address and contact information		X	X		X	X
17.	Name of source establishment, its civic address and contact information		X	X		X	X
18.	Registration number of source establishment, clearly labelled as such		X	X		X	X
19.	Name of transplant establishment, its civic address and contact information			X			X
Storage information							
20.	Statement "Human organ for transplant"			X			X
21.	Handling instructions for storage and for storage during transportation			X			X

Additional information required

33. A registered establishment that imports and distributes, or that only distributes, a cell or tissue must ensure that the following information is added to that required by sections 30 and 31: (a) on the exterior label and in the package insert, the name of the establishment, its civic address and contact information; and

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

QUARANTINE

Quarantine — cells and tissues

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

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

Additional requirement — live donors of tissue

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

STORAGE

Storage limits

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

Storage location

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

Storage during transportation

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

Segregation — tissues

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

Segregation — transmissible disease agents and markers

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

EXCEPTIONAL DISTRIBUTION

Conditions

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

- (a) a cell, tissue or organ that has been determined safe for transplantation is not immediately available;

(b) the transplant physician or dentist, based on their clinical judgement, authorizes the exceptional distribution; and

(c) the transplant establishment obtains the informed consent of the recipient.

Notice in source establishment's records

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

Notice in transplant establishment's records

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

Contents of notice

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

(a) the name of the transplanted cell, tissue or organ;

(b) the provisions of these Regulations with which the cell, tissue or organ is not in compliance at the time of its distribution;

(c) the justification for the distribution that formed the basis for the transplant physician's or dentist's decision to authorize it;

(d) the name of the source establishment that distributed the cell, tissue or organ;

(e) the name of the transplant establishment and of the transplant physician or dentist who authorized the distribution; and

(f) the time and date of the written authorization of the distribution and a copy of the authorization signed by the transplant physician or dentist.

Follow-up

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

ERROR, ACCIDENT AND ADVERSE REACTION INVESTIGATION AND REPORTING

ERRORS AND ACCIDENTS

Required action

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

(a) determine the donor identification codes of all implicated cells, tissues and organs;

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

Written notice

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

Action by source establishment

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

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

Contents of notice

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

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

When no investigation necessary

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

Action on receipt of notice

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

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

ADVERSE REACTIONS

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.

INVESTIGATIONS AND REPORTING

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.

RECORDS

Record quality

55. Records kept by an establishment must be accurate, complete, legible and indelible.

Donor identification code — source establishment

56. (1) A source establishment must assign a donor identification code to each donor of a cell, tissue or organ for which it has responsibility.

Donor identification code — all establishments

(2) Every registered establishment and transplant establishment must ensure that the donor identification code is a component of its records system.

Requirement

57. An establishment's records must contain information with respect to all cells, tissues and organs that it processes, distributes, imports or transplants that identifies

- (a) the establishment from which it receives the cells, tissues and organs; and
- (b) all establishments to which it distributes the cells, tissues and organs.

Shipping documents

58. An establishment's records must include all shipping documents with respect to cells, tissues and organs that it ships to another establishment.

Source establishment records

59. The source establishment must keep records with respect to cells, tissues and organs that it processes that contain at least all of the following information:

- (a) the donor identification code;
- (b) documentation showing completion of the donor suitability assessment;
- (c) a description of the cells, tissues and organs retrieved from the donor;
- (d) if applicable, the name of any source establishment from which it received a donor referral or to which it made a donor referral;
- (e) the name of the retrieval establishment;
- (f) documentation of all processing activities;
- (g) the notice of exceptional distribution, if any; and
- (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.

Transplant establishment records

60. The transplant establishment must keep records with respect to cells, tissues and organs that it transplants that contain at least all of the following information:

- (a) a description of the transplanted cells, tissues or organs;
- (b) the donor identification code;
- (c) the registration number of the source establishment;
- (d) the notice of exceptional distribution, if any, and confirmation that the donor suitability assessment was completed as required by section 42;
- (e) information that allows the identification of the recipient; and
- (f) documentation of any errors, accidents and adverse reactions and their investigation in connection with those cells, tissues or organs and any corrective action taken.

Establishments to cooperate

61. An establishment must provide the source establishment and the transplant establishment with all of the information described in sections 59 and 60, respectively, that it possesses to complete the establishment's records.

Retention — 10 years after transplantation

62. (1) An establishment must keep the following records for at least 10 years after the date of transplantation, if known, or for at least 10 years after the date of distribution, final disposition or expiry of the cell, tissue or organ, as the case may be, whichever is the latest:

- (a) the records described in section 57;
- (b) the records described in section 59, except paragraph (h);
- (c) the records described in section 60, except paragraph (f); and
- (d) the record of destruction or other disposition of the cell, tissue or organ, if applicable.

Retention — 10 years after record creation

(2) An establishment must keep the following records for 10 years after the date of their creation:

- (a) the records described in paragraphs 59(h) and 60(f); and
- (b) reports of audits conducted under section 76, if applicable.

Retention — employee records

(3) An establishment that distributes cells, tissues or organs must keep records of the qualifications, training and competency of its employees for 10 years after the time an individual ceases to be an employee of the establishment.

Retention — standard operating procedures

(4) An establishment that distributes cells, tissues or organs must keep a copy of every version of its standard operating procedures for 10 years after they are superseded by a new version.

Storage of records

63. An establishment that distributes cells, tissues or organs must store records in a location that has appropriate environmental conditions and that is secure against the entry of unauthorized persons.

PERSONNEL, FACILITIES, EQUIPMENT AND SUPPLIES

PERSONNEL

Sufficient number and qualifications

64. (1) An establishment that distributes cells, tissues or organs must have sufficient personnel who are qualified by education, training or experience to perform their respective tasks to carry out the establishment's activities.

Competency

(2) An establishment that distributes cells, tissues or organs must have a system for the orientation and training, both initial and ongoing, of personnel and for the evaluation of their competency.

FACILITIES

Requirements

65. The facilities of an establishment that distributes cells, tissues or organs must be constructed and maintained to permit all of the following:

- (a) the carrying out of all of its activities;
- (b) the efficient cleaning, maintenance and disinfection of the facilities in a way that prevents contamination and cross-contamination;
- (c) environmental and microbiological monitoring and control appropriate to the areas where its activities are carried out; and
- (d) controlled access to all areas where its activities are carried out.

EQUIPMENT AND SUPPLIES

Requirements — equipment

66. An establishment that distributes cells, tissues or organs, in carrying out its processing and storage activities, must use equipment that is cleaned and maintained and, whenever applicable,

- (a) qualified for its intended purpose;
- (b) calibrated;
- (c) disinfected or sterilized before each use; and

(d) requalified or recalibrated, as appropriate, after any repair or change is made to it that results in a change to its specifications.

Requirements — storage equipment

67. An establishment that distributes cells, tissues or organs that uses equipment to store cells, tissues or adjunct vessels that are not used immediately in organ transplantation must ensure that the equipment maintains appropriate environmental conditions.

Processing supplies

68. An establishment that processes cells, tissues or organs must use qualified supplies for those activities that could affect the safety of the cells, tissues or organs, and must store solutions, reagents and other supplies under appropriate environmental conditions.

Cleaning supplies

69. An establishment that processes cells, tissues or organs must ensure that it uses supplies for cleaning, maintenance, disinfection or sterilization that do not react with, or that are not absorbable by, the cells, tissues or organs.

QUALITY ASSURANCE SYSTEM

GENERAL

Application

70. Sections 71 to 76 apply only to establishments that distribute cells, tissues or organs.

Quality assurance system required

71. An establishment must ensure that it has a quality assurance system in place that complies with the requirements of these Regulations for all activities that it carries out.

STANDARD OPERATING PROCEDURES

Standard operating procedures required

72. An establishment must have standard operating procedures with respect to the safety of cells, tissues and organs for all activities that it carries out.

Requirements

73. The standard operating procedures must meet all of the following requirements:

- (a) be in a standardized format;
- (b) be approved by the medical director or scientific director;
- (c) be available for use at all locations where the relevant activities are carried out;
- (d) have any changes to the procedures approved by the medical director or scientific director before being implemented; and
- (e) be kept up-to-date.

Routine review

74. (1) An establishment must review its standard operating procedures every two years and again after any amendment to these Regulations.

Supplementary review

(2) An establishment that receives a summary of a final report of an error, accident or adverse reaction investigation or the report of an audit either of which reveals a deficiency in a standard operating procedure must review that procedure.

Records of compliance

75. An establishment must keep records that demonstrate that it has implemented its standard operating procedures.

Audits

76. An establishment must conduct an audit every two years of the activities that it carries out to verify that those activities comply with these Regulations and with its standard operating procedures, by a person who does not have direct responsibility for the activities being audited.

POWERS OF INSPECTORS

Taking photographs

77. An inspector may, in the administration of these Regulations, take photographs of any of the following:

- (a) any article that is referred to in subsection 23(2) of the Act;
- (b) any place where the inspector believes on reasonable grounds that any article referred to in paragraph (a) is processed; and
- (c) anything that the inspector believes on reasonable grounds is used or is capable of being used in the processing of any article referred to in paragraph (a).

TRANSITIONAL PROVISION

Processed within 5 years before registration

78. (1) Subject to subsection (2), the following establishments may import, distribute or transplant, as the case may be, cells and tissues that were processed within five years before the day on which these Regulations are registered:

- (a) a registered establishment; and
- (b) a transplant establishment that does not distribute cells or tissues.

Prohibition

(2) An establishment may not import, distribute or transplant, as the case may be, cells or tissues under subsection (1) unless the requirements of subsection 56(2) and section 57 are met.

COMING INTO FORCE

Six months after registration

79. (1) These Regulations, except subsection 26(1), come into force six months after the day on which they are registered.

Exception

(2) Subsection 26(1) comes into force one year after the day on which these Regulations are registered.

Transitional provision

(3) Section 78 ceases to be in force five years after the day on which these Regulations are registered.

REGULATORY IMPACT ANALYSIS STATEMENT
RÉSUMÉ DE L'ÉTUDE D'IMPACT DE LA RÉGLEMENTATION

(This statement is not part of the Regulation.)

(Ce résumé ne fait pas partie du règlement.)

Department or Agency

Health

Ministère ou organisme

Santé

Title of Proposal

Project No. 1363

*Safety of Human Cells, Tissues and Organs
for Transplantation Regulations*

Amendments to be done to
Medical Devices Regulations
and
Schedule D of the *Food and Drugs Act*

Titre du projet

Projet no. 1363

*Règlement sur la sécurité des cellules, tissus
et organes humains destinés à la
transplantation*

Modifications à apporter au
Règlement sur les instruments médicaux
et
Annexe D de la *Loi sur les aliments et
drogues*

Statutory Authority

Food and Drugs Act,
c. F-27, subsection 30(1)

Fondement législatif

Loi sur les aliments et drogues,
ch. F-27, paragraphe 30(1)

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Minister of Health / Ministre de la Santé

REGULATORY IMPACT ANALYSIS STATEMENT

(This statement is not part of the Regulation.)

Description

The purpose of this regulatory initiative is to minimize the potential health risks to Canadian recipients of human cells, tissues and organs (CTO). The *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* (CTO Regulations) address safety in the processing and handling of these products, resulting in improved protection of the health and safety of Canadian transplant recipients.

It is important to acknowledge the life-saving / life-enhancing gifts that make possible the transplantation of human cells, tissues or organs. Health Canada recognizes this noble sacrifice, which should not be considered diminished in any way by the use of regulatory language, necessary under the constraints imposed by the *Food and Drugs Act* (F&DA). By regulating all establishments and individuals in Canada that handle, process, distribute or import human CTO, these standards-based regulations for CTO will enable Health Canada to play an active role in realizing the intended benefit of these gifts, and contribute to fulfilling its mandate to maintain and improve the health of Canadians.

The CTO regulations incorporated the following instruments in their development: the safety standards upon which they are based; a risk management approach in their design and enforcement; provinces, territories and transplantation experts have been engaged in extensive consultations during the course of their development. These regulations also deliver on the Government's commitment in the Budget for 2005 to continue to invest in health care, through direct support of therapeutic product safety.

The CTO Regulations were pre-published in *Canada Gazette*, Part I on December 10, 2005 for a 75-day comment period. In response to publication, Health Canada received questions of clarification from fifteen organizations, as well as thirty-two (32) sets of comments and recommendations from organizations belonging to the domestic and international CTO community. Comments and recommendations received during, and after the close of, the 75-day comment period were crucial in the further development of these regulations. Health Canada's responses to these questions and recommendations varied from personal contact via email or phone contact for clarifications, further development of guidance for clarification and changes to the CTO Regulations. Any change made to the CTO Regulations, while not compromising the health and the safety of Canadian recipients, resulted in less onerous requirements on the CTO community. All changes to the regulations, minus those of an editorial nature, are outlined in the Consultation section of this RIAS.

As the CTO Regulations are implemented, a consequential amendment to Schedule D to the F&DA is also required. The CTO Regulations will cover cord blood and peripheral blood when used as a source of lymphohematopoietic cells intended for use in transplantation, while cord blood and peripheral blood intended for transfusion will continue to be regulated in Schedule D to the F&DA.

The *Medical Devices Regulations* (MDR) will also be amended upon implementation of the CTO Regulations. The intention is to limit the scope of the MDR to Medical Devices manufactured from or incorporating animal or human cells or tissues. To allow for an appropriate transition, it is proposed that heart valves and dura mater will remain under the MDR until further analysis and consideration of appropriate regulatory oversight has taken place.

Need for Regulation

Health Canada is the federal authority that regulates the safety, efficacy and quality of therapeutic products used in Canada pursuant to the F&DA. To date, there has been no consistent regulatory approach to maximize the safety of human CTO. Certain CTO are currently regulated under the MDR (e.g. dura mater and heart valves), the FDR (e.g. blood) and *Processing and Distribution of Semen for Assisted Conception Regulations* (e.g. semen for assisted conception), three separate sets of regulations under the F&DA. For other tissues and for organs, there are currently no specific regulations under the F&DA. In addition, there has been a lack of specific safety standards, compliance monitoring and enforcement activities, and adverse event reporting for most establishments handling/processing CTO that takes into consideration the unique characteristics of these products.

Challenges

Instituting an effective approach, one that is both consistent and comprehensive, has proven challenging for a variety of reasons. Canadian establishments engaged in handling/processing CTO for transplantation currently employ multiple sets of voluntary standards that vary in their level of comprehensiveness. Other issues include overlapping federal/provincial jurisdiction and the various types of and uses for tissues, all of which result in a very complex regulatory environment. For these reasons, federal regulatory intervention in the CTO community has long been recommended by various stakeholders, including industry and government.

Health Canada's Response - National Standards

In 1996, Health Canada began to address the need for regulation, and thereby the concerns of stakeholders, by striking a working group of independent experts to develop safety standards for CTO. In 2000, Health Canada contracted with the Canadian Standards Association (CSA) to facilitate the publication of the resulting National Standards designed to maximize the safety, quality and performance of CTO for transplantation. The Standards Council of Canada has accredited the CSA as the standards development organization in Canada. The CSA Technical Committee, which includes representatives from Health Canada, provincial and territorial governments, health professional groups and CTO stakeholders, was tasked with the development of the standards. Following extensive collaboration with experts in the field, federal and provincial governments and interested stakeholders, the National Standards were published in June 2003. This marked the initiation of the development of the new standards-based regulatory framework for CTO.

The time required to develop the National Standards reflects the wide variety of CTO products as well as the technical complexity of the processes utilized by the CTO industry. The CSA Technical Committee was responsible for the simultaneous development of the general and subset standards, adding to the scope of the project. In addition, members of the CSA Technical Committee volunteer their time rather than work exclusively on the standards, all of which contributed to lengthen the time required for their development.

To meet the requirement for public consultation in the development of National Standards, the CSA posted each of the draft standards on its website for a 60-day comment period, in addition to distributing copies to individuals/organizations that expressed an interest. Over 1,000 comments were received through this public review process, and these comments were referred to the CSA Technical Committee for consideration and possible incorporation into the standards.

As they were drafted through a consensus-development process, the National Standards have now met the requirements of the Standards Council of Canada, having provided multiple opportunities for Canadians to express their points of view and/or concerns about these standards. Extensive consultation with key stakeholders during the drafting process provided transplantation programs with a significant familiarity with the standards' requirements. In fact, during these consultations, it was the CTO community that again identified the need for, and recommended the creation of, a regulatory framework for CTO.

The National Standards form the basis for the safety requirements that have been incorporated into the CTO regulatory framework. The CTO Regulations directly reference sections of the General Standard CAN/CSA Z900.1, entitled Cells, Tissues, and Organs for Transplantation and Assisted Reproduction: General Requirements, along with four of the five subset standards for specific organ and tissue types (i.e. the standards for lymphohematopoietic cells, perfusable organs, tissues, and ocular tissues), thus making them mandatory. [The Z900 package of the National Standards may be obtained by calling 1-800-463-6727 or from the following website: <http://www.csa-intl.org/onlinestore/>]. It is important to note that the CSA standards speak to various aspects of the donation and transplantation process. However, as Health Canada's authority is limited to the safety of cells, tissues and organs, every section that is referenced in the regulations is related to the safety of CTO. Sections of the standards that relate to practice of medicine are not referenced in these regulations as practice of medicine falls under provincial jurisdiction.

Interim Measures

While the National Standards were being developed, Health Canada recognized the need for interim measures. In January of 2003, Health Canada issued a Directive entitled "Technical Requirements to address the Safety of Human Cells, Tissues and Organs for Transplantation" (Directive) and its corresponding Guidance Document entitled "Basic Safety Requirements for Human Cells, Tissues and Organs for Transplantation" (Guidance Document). The Directive and Guidance Document were updated in 2005 to reflect CSA changes to the testing requirements. [The Directive and Guidance Document are posted on the Health Canada website: http://www.hc-sc.gc.ca/dhp-mps/brgtherap/reg-init/cell/cto_directive_e.html]

These documents provide guidance for donor screening, donor testing, CTO retrieval/collection, processing, preservation, packaging and labelling, storage, quarantine, record keeping, importation, distribution, transplantation, adverse reaction monitoring and error and accident reporting and investigation. Pursuant to the Directive, CTO which are not processed in accordance with the basic standards of safety will be considered by Health Canada to be “manufactured, prepared, preserved, packaged and stored under unsanitary conditions; to be adulterated; or to have the potential to cause injury under normal conditions of use”. However, at such time as the CTO Regulations come into force 6 months after their registration, the requirements in the Directive and Guidance Document will be superseded by those found in the CTO regulations.

National Review

In March 2003, following the release of the Directive and Guidance Document, Health Canada initiated a National Review of establishments handling and/or processing CTO for transplantation. The objective of the National Review is to assess establishments’ adherence to basic safety requirements, as specified in the Directive and Guidance Document.

The National Review consists of two stages: a documentation stage during which Health Canada requests supportive information/documentation from programs involved in the handling and/or processing of CTO; and a compliance monitoring stage, during which Health Canada inspects establishments to assess their adherence to basic safety requirements. The National Review has allowed Health Canada to gain a better understanding of the CTO industry in Canada. It has also provided data that can be used to evaluate the overall risks related to CTO for transplantation and, therefore, can contribute to the institution of the appropriate regulatory adverse reaction reporting and compliance monitoring and enforcement mechanisms. An equally important aspect of the National Review is the opportunity it affords Health Canada to demonstrate to establishments the importance of adhering to basic safety standards. Until these regulations are in place 6 months after their registration, the Directive and Guidance Document will provide interim guidance to Canadian CTO establishments, while the ongoing National Review (both stages) will continue to monitor the compliance of these establishments with basic safety requirements.

Regulatory Framework for CTO

The CTO Regulations were drafted pursuant to the F&DA, and represent Phase I of the intended regulatory framework. The National Standards encompass all activities related to transplantation, which include aspects of product safety, as well as issues around practice of medicine. However, Health Canada may only regulate activities that fall under its authority to regulate the safety, efficacy and quality of therapeutic products used in Canada. Thus based on the National Standards, the regulations set out basic safety requirements with respect to donor screening, donor testing, collection/retrieval, processing, preservation, packaging, labelling, storage, quarantine, record keeping, distribution, importation, error, accident and adverse reaction monitoring and reporting and investigation. Wherever possible, relevant sections of the

standards (i.e. areas under federal jurisdiction and mandatory requirements) are referenced in the regulations.

Health Canada is responsible for delivering national compliance monitoring and enforcement programs for all health products as well as for conducting surveillance of errors, accidents and adverse reactions. Therefore, Health Canada has the authority to regulate the safety requirements specifically referenced in the regulations related to the activities listed above. This does not mean that other activities related to the transplantation of CTO are not important or monitored. Health Canada is responsible for regulating the safety of CTO used in transplantation, while the safety of transplantation itself is shared among provincial and territorial governments, trade associations, health professionals and their associations, and consumers and their associations.

The regulatory framework for CTO will be introduced in two phases, so as to allow the specific safety regulations to be given priority. The main objective of the Phase I regulations is to maximize the safety of CTO, by clearly stipulating the safety requirements adopted from the National Standards, thus making them mandatory. Referencing the National Standards will provide a consistent and safety-focussed regulatory framework that will minimize the risks to Canadians associated with CTO for transplantation.

The other key elements of the regulatory framework include compliance monitoring and enforcement, as well as error, accident and adverse reaction monitoring and reporting strategies. Phase I introduces a registration mechanism for establishments that handle, process, distribute or import human CTO. It will require all establishments to monitor errors, accidents and adverse reactions and report these to the source establishment, who in turn must report to Health Canada errors and accidents that could lead to a serious adverse reaction involving the transmission of an infectious disease or disease agent, and unexpected serious adverse reactions suspected of involving the transmission of an infectious disease or disease agent.

Phase II of the regulatory framework for CTO will include more comprehensive compliance monitoring and enforcement provisions, and surveillance and adverse reactions reporting strategies. In Phase II, heart valves and dura mater (lining of the brain) will fall under the CTO Regulations. At that time, an amendment to the Phase I regulations will be required to incorporate heart valves and dura mater into the CTO Regulations, as well as a simultaneous amendment to remove them from the MDR.

Scope of the CTO Regulations for Phase I

These regulations will apply to human organs and minimally manipulated cells and tissues intended for homologous use in transplantation in another individual.

During Phase I, the regulatory framework will not apply to the following therapeutic products:

- Cells and tissues that are more than minimally manipulated;

- CTO that are for non-homologous use (i.e. CTO used for a purpose other than its original function);
- Cells and tissues that are for autologous use (i.e. cells or tissues retrieved, modified and later returned to the same individual);
- tissues and cells, (except for lymphohematopoietic cells, that are derived from bone marrow, peripheral blood or cord blood and islet cells), that have a systemic effect and depend on their metabolic activity for their primary function;
- Medical Devices that contain cells or tissues that are used in investigational studies in humans, currently regulated under Part 3 of the MDR;
- CTO that are used in clinical trials in humans, currently regulated under Division 5 of the F&DR;
- whole blood and blood components for transfusion, including cord blood for transfusion currently regulated under the FDR and Schedule D to the F&DA;
- cells and tissues regulated under the *Assisted Human Reproduction Act* or any of its regulations;
- semen regulated under the *Processing and Distribution of Semen for Assisted Conception Regulations*; and
- cells and tissues that are currently regulated under the MDR (e.g. heart valves, dura mater, demineralized bone, wound covering containing human cells).

Registration of CTO Establishments

The main compliance monitoring and enforcement feature for Phase I is a registration scheme for establishments responsible for processing, distribution and importation of CTO. All source establishments and establishments that distribute or import will be required to apply for registration with Health Canada. It is also important to note that in order to comply with the CTO Regulations, Canadian establishments may only import cells and tissues that have been processed by establishments registered with Health Canada.

The registration application contains a description of the CTO processed, distributed or imported by the establishment and the types of activities it carries out or for which it is responsible. In addition, the registration form contains a certification of compliance with the CTO Regulations that must be signed by the medical or scientific director, depending on the establishment's organizational structure. If it is deemed that the information provided is sufficient and satisfactory, the Minister will issue a registration number to the establishment that is valid for a period of up to 2 years. The registration number is valid until December 31 in the year after the year in which it was issued. [The registration form will be posted on the Health Canada web site: http://www.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/cell/index_e.html]

The Minister has the power to refuse to issue a registration number if there is reason to believe that any information provided is false, misleading, inaccurate or incomplete. The Minister also has the power to suspend or revoke a registration number through established process if there is reason to believe that the establishment is not in compliance with the CTO Regulations, and to cancel immediately should the noncompliance pose a sufficiently serious threat to health and safety. Any change in the information provided on the registration

application, including addition or cessation of activities listed, must be communicated to the Minister. This registration scheme will provide a comprehensive list of all establishments involved in handling/processing CTO in Canada, the activities they perform and the establishments to whom they distribute.

Source Establishment

The source establishment plays a pivotal role in determining the safety of CTO, through its responsibility for the oversight of donor screening, donor testing, donor suitability assessment, preparation, preservation, packaging and labelling, quarantine, banking, whether it performs these functions or they are performed by another establishment on its behalf. An additional requirement is that establishments must have a quality assurance system in place to control the oversight of all the activities for which it is responsible, including the investigation of all errors, accidents and adverse reactions.

Processing

Processing includes the screening, testing and suitability assessment of donors, as well as the retrieval, preparation and preservation, packaging and labelling, quarantine, and banking of CTO. The regulations reference specific sections of the National Standards which outline the basic requirements for donor screening and testing listed in the general standard and/or specific subset standards. The exclusion criteria component of the donor suitability assessment also references the appropriate section of the National Standards, by tissue/organ type. Establishments that distribute CTO are also required to have validated written standard operating procedures (SOP) for all activities performed in their establishment.

Packaging and Labelling

Appropriate packaging and labelling are essential components of the safety and accurate identification of CTO. Packaging material must be inspected before use to ensure they are free from damage. The information requirements for interior and exterior labels and package inserts are listed in the tables to the labelling sections of the regulations, and must be in either English or French. These requirements vary according to whether the label is for a cell, tissue or organ and whether cells and tissues are banked. For example, cells or tissues intended for banking must have an expiry date indicated on the label. It is also important to note that registration numbers are required on some of the labels. This will provide the user with assurance that the product originated from a registered source establishment.

Storage

Establishments that distribute must store CTO under defined and controlled environmental conditions. An establishment that stores and distributes CTO must also observe their validated maximum storage periods. The documented evidence that support the validated maximum shelf life for CTO must be available. Access to storage area must be restricted to designated personnel. Tissues intended for autologous use must be segregated from those intended for

allogeneic use. CTO that are untested or are reactive or positive for transmissible disease agents or markers must be segregated from all other CTO.

Quarantine

The CTO Regulations stipulate that cells and tissues that have not been tested or have tested positive for applicable infectious disease markers specified in the donor suitability assessment section, must be segregated or quarantined from screened cells and tissues that tested negative. These cells and tissues remain in quarantine until infectious disease and bacteriological testing is completed, the results are negative or non-reactive, and the results have been documented, reviewed and considered acceptable by the medical or scientific director.

Cells and tissues that are the subject of an investigation of any error, accident or adverse reaction must also be segregated from other cells and tissues until such time as the results of the investigation deem the CTO suitable for transplantation. In addition, as new infectious diseases emerge, a source establishment must quarantine all of its banked cells and tissues until they are tested for that disease agent or marker.

Exceptional Distribution

A need was identified for a mechanism to allow for the distribution of a CTO that may not meet all of the requirements of these regulations, when no fully compliant CTO is available. The CTO regulations provide that, under similarly exceptional circumstances, a source establishment may distribute CTO that have not been processed in accordance with these regulations, provided that the transplant physician or dentist authorizes the distribution. In addition, the recipient must have given his/her informed consent. After the exceptional distribution of a CTO, the source establishment must still complete the donor suitability assessment and carry out any appropriate follow-up testing. In most cases, the exceptional distribution criteria can only be met by life-saving / life-enhancing transplantations.

A notice of exceptional distribution must indicate the section of these regulations with which the CTO does not comply, the transplant physician's or dentist's justification for the distribution, the name of the transplanted CTO, the name of the source establishment that distributed the CTO, the name of the transplant establishment, the name of the transplant physician or dentist who authorized the distribution, the time and date of the authorization for distribution. The notice must be retained in the files of both the source and transplant establishment.

Errors and Accidents

The regulations require that establishments must report to the source establishment all known or suspected errors or accidents that occur during processing that are associated with a CTO. They must identify and quarantine the implicated CTO. Furthermore, establishments must notify all other establishments in the supply chain including any establishment that either supplied, processed, or to which it distributed the implicated CTO of the possible occurrence of an error and accident during the processing of CTO that may have compromised the safety of

CTO in their possession. The source establishment(s) must initiate the investigation and advise all relevant establishments to quarantine all implicated CTO in their possession until further notice. A timely written confirmation is required for any verbal notice.

Adverse Reactions

Adverse reaction surveillance is an essential component of a regulatory framework for therapeutic products to help identify risks to the supply chain and to help ensure appropriate action is taken to minimize future risk. The CTO Regulations require that all establishments report unexpected adverse reactions to the source establishment that processed the relevant CTO. In their report to the source establishments, all establishments must identify the suspected transmissible disease or disease agent if known, the implicated CTO, and provide a description of the adverse reaction. Establishments are required to quarantine all implicated CTO in their possession and notify all establishments to which it distributed the CTO in question.

Investigations and Reporting to Health Canada

Due to the source establishment's strategic location in the supply chain, the CTO Regulations place the onus on source establishments to investigate all errors, accidents and adverse reactions. The source establishment must notify the Minister in writing that an adverse reaction or a suspected error or accident that could lead to a serious adverse reaction involving the transmission of an infectious disease or disease agent has occurred and must confirm that an investigation has been initiated in that respect. Within 24 hours of the start of an investigation, the source establishment must report to Health Canada the name of the suspected infectious disease/agent, and the type of CTO. Nevertheless, this requirement to report to Health Canada does not replace the establishment's requirement to report designated infectious diseases to Provincial/Territorial Health Authorities.

The source establishment is required to notify all establishments to which it distributed or received the implicated CTO that it has initiated an investigation, as well as the initial results and the final outcome of the investigation. To facilitate this process, establishments must provide the source establishment with any information in their possession that could assist in the investigation. Furthermore, the source establishment must report to Health Canada any new information about the suspected error, accident or serious unexpected adverse reaction and the steps taken in the investigation 15 days of initiating the investigation and every 15 days until the final report is submitted. The final report must describe the results of the investigation, the final disposition of the CTO in question and any corrective action taken.

Records

Establishments that distribute CTO are required to have written standard operating procedures for all their critical activities and keep records in locations secure against unauthorized persons. In addition, the source establishment is responsible for assigning a donor identification (ID) code to the CTO when it is retrieved/collected. All subsequent handlers of the

CTO, including the transplant establishment, must retain the necessary records to be able to trace a CTO from the donor to the final recipient.

Source establishments must keep records that contain the donor ID code, documentation demonstrating completion of donor suitability assessment; a description of CTO; the name of the retrieval establishment; documentation of all processing steps including equipment and instruments used; documentation of any adverse reaction, error or accident related to the CTO, the results of their investigation and any corrective action taken; and the notice of exceptional distribution, if any.

Transplant establishments must keep records that contain a means to identify the recipient; the donor ID code; a description of CTO transplanted; documentation of any adverse reaction, error or accident related to the CTO, and notice of exceptional distribution, if any.

Retention Period for Records

All records must be kept for a minimum of 10 years after the date of transplantation or final disposition, whichever is latest.

Personnel

Establishments that distribute CTO are required to have sufficient personnel with the qualifications necessary to perform their assigned duties. Personnel may be qualified by education, training or experience (or a combination thereof). These establishments must have a system in place to provide personnel with initial and ongoing training and to evaluate their competency.

Facilities

Establishments that distribute CTO are required to have facilities that are constructed and maintained so as to allow for the performance of all its activities, the efficient cleaning and disinfection to prevent contamination or cross-contamination, environmental and microbiological monitoring and control in all areas and controlled access to all areas where its activities are carried out.

Equipment

All establishments that distribute CTO must use equipment that is cleaned and maintained, and where applicable, qualified for its intended purpose, calibrated, disinfected or sterilized before each use and requalified or recalibrated after any repair or change that may result in a change to its specification. Any equipment used to store cells, tissues or organs must maintain the appropriate environmental conditions.

Processing Supplies

An establishment that processes CTO must store solutions, reagents and other supplies under appropriate environmental conditions. Establishments must also ensure that supplies used for cleaning, maintenance, disinfection or sterilization do not react with, or are not absorbable by, the CTO.

Quality Assurance System

Establishments that distribute CTO are required to have a quality assurance system in place that complies with the requirements of the regulations and enables them to carry out all their activities. An important component of a quality assurance system is the standard operating procedures (SOP), which must be kept current, be approved by the medical or scientific director, be available where relevant activities are carried out and have all changes approved by the medical or scientific director before they are implemented. Establishments are required to review SOP every two years and again after any changes to the CTO Regulations.

Transitional Provisions

Cells and tissues that were processed within five years before the regulations are registered can only be imported and/or distributed by a registered establishment. CTO processed prior to the coming into force of the CTO Regulations must meet certain safety requirements, namely that every registered and transplant establishment must ensure that the donor identification code is a component of its record system, and that all establishment's records must contain information with respect to all CTO that it processes, distributes, imports or transplants that identifies both the establishment from which it received the CTO, and all establishments to which it will be distributed. These provisions will remain in effect for five years.

Furthermore, Health Canada will continue to exercise its authority under Sections 8 and 19 of the *Food and Drugs Act* to prohibit the distribution of products that 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.

International Perspective

Other international regulatory agencies have similar regulations and/or guidelines for cells and tissues. Health Canada's CTO Regulations harmonizes well with other nations' policies to protect the health of recipients through oversight of the assessment of donor suitability, procurement, and processing of CTO for transplantation. For example, the United States' phased-in implementation and the use of a registration scheme, coupled with an adverse reaction reporting requirement, is similar to the Canadian CTO Regulations. International harmonization provides confidence that CTO obtained from these countries should meet the same high safety standards set by the CTO Regulations, and enables an uninterrupted supply of safe CTO for transplantation.

Due to our development of the National Standards for CTO, Canada is perceived as a regulatory leader in the field of transplantation safety. This was demonstrated by the World Health Organization (WHO)'s request for Canada to host the First Global Consultation on Regulatory Requirements for Human Cells and Tissues for Transplantation in Ottawa, November 29 to December 1, 2004. In addition, Australia has requested permission to use our National Standards in the development of their regulations for cells and tissues, furthering both our image as leaders in the regulation of CTO as well as international harmonization.

Alternatives

Both regulatory and non-regulatory options were explored, including: 1-the status quo; 2-voluntary standards; 3- waiting until all elements of the full framework could be implemented at the same time; and the chosen alternative 4-implementing a safety standards-based framework in two phases.

Alternative 1

The status quo option was quickly rejected. The current F&DA and associated regulations treat CTO in an inconsistent manner. Some human tissue-derived products are classified as Medical Devices under the MDR. However, organs and minimally manipulated tissue products have never been treated as Medical Devices, neither by the transplantation industry nor by Health Canada. While CTO are currently regulated as drugs under the general provisions of the F&DA and are subject to the FDR, it is recognized that many of the regulations that apply to drugs cannot apply to organs or minimally manipulated cells and tissues.

For the above reasons, it was determined that Canada needs a framework that will encompass organs and minimally manipulated cells and tissues intended for transplantation. This decision recognized that human CTO products are therapeutic products distinguished from traditional pharmaceutical products or Medical Devices. Also, stakeholders' expectations of a standards-based regulatory framework for CTO would not be met with this alternative.

Alternative 2

The option of voluntary standards was also rejected. In a 2001 survey of all facilities handling and/or processing CTO intended for transplantation in Canada, nearly one third of all the establishments admitted to not following any recognized standards, (e.g. American Association of Tissue Banks, Eye Bank Association of America, European Association of Tissue Banks, etc.). Moreover, although the majority of facilities use some standards to maximize safety, it was not easy to verify to what extent they complied with the standards they claimed to follow. Therefore, adding new voluntary national standards would not provide the necessary assurance that the establishments meet all the requirements listed in the standards, and would not maximize the safety of CTO available to Canadians. In this regard, Health Canada could not fulfill its mandate by implementing voluntary standards. In addition, stakeholders' expectations of a standards-based regulatory framework would once again not be met with this alternative.

Alternative 3

The third option, which advocated waiting until a complete regulatory framework was ready for implementation, was also rejected. Although early in the developmental process, implementation of a full regulatory framework was intended, Health Canada changed its strategy to a two-phased approach, thus allowing the specific safety regulations to be given priority. The need was recognized for a registration (or similar) scheme to enhance the picture of handling and processing of CTO in Canada before deciding on a full compliance monitoring and enforcement regime. A further consideration was the fact that the CTO community consists of many varying establishments never before regulated, indicating that a step-wise approach to regulation was preferable.

Alternative 4 - CTO Regulations

The fourth and chosen option was to develop regulations that incorporate the basic safety requirements for CTO by direct reference to the National Standards and implement these regulations in two phases. Phase I consists of standards-based safety requirements for CTO, coupled with the reporting of errors, accidents and adverse reactions known to have resulted or with the potential to result in infectious disease transmission, and a registration/certification of compliance for establishments that process, distribute or import CTO; Phase II will add a more comprehensive compliance monitoring and enforcement, error, accident and adverse reaction monitoring and reporting schemes. This two-phased approach was considered the best option because it allows the more critical safety components of the regulations to be implemented more quickly, thus enabling Health Canada in its mandate of safeguarding CTO products available for transplantation in Canada. It also allows sufficient time to consult with stakeholders on compliance monitoring and enforcement options available for Phase II, to incorporate their comments, and to address their concerns in the final regulations. Consultations provide an additional opportunity to identify any regional issues that should be addressed by the new regulatory framework.

Benefits and Costs

This option will result in the following benefits and costs. They have been presented below according to sector.

Establishments involved in the transplantation of CTO

To determine the estimated costs to establishments, Health Canada contracted Goss Gilroy Inc (GGI) in 2003 to conduct a benefit-cost analysis of the National Standards for CTO and the National Standards for Blood and Blood Components. For the purposes of this RIAS, the results presented will only pertain to the analysis conducted for CTO. The GGI survey was to determine the incremental costs that establishments would incur to bring their establishments into compliance with the standards and to maintain them at that level for the next 20 years.

Costs

Since the regulations are based on the National Standards, the results of the benefit-cost analysis conducted by GGI provide a good estimate of the costs required by the establishments to meet the safety-based requirements of the regulations. However, since some of the requirements in the National Standards are not covered in the CTO Regulations, it is fair to conclude that the cost estimate of the National Standards provide a higher estimate than the actual costs of the CTO Regulations. In addition, some of the sections in the National Standards overlap between federal and provincial jurisdiction and it was unrealistic to ask respondents to distinguish between federal or provincial jurisdiction. For example, one respondent could be aware that to meet the standards he would require one additional staff. That person may work on many activities covered by the National Standards, making it difficult to determine the exact percentage of time the person may work to meet the requirements that fall under federal jurisdiction.

Also, since 2003, it is expected that many establishments will have already invested resources in order to come into compliance with the National Standards and Health Canada's Directive and Guidance Document. The National Review of establishments that handle/process CTO for transplantation has further emphasized the need for establishments to follow the National Standards and comply with the Directive and Guidance Document. Some establishments have achieved voluntary accreditation with the Eye Bank Association of America (EBAA), the American Association of Tissue Banks (AATB), the Foundation for the Accreditation of Hematopoietic Cell Therapy (FAHCT), and the American Society for Histocompatibility and Immunogenetics (ASHI), which have similar safety requirements for cell and tissue processing. Thus, for the purpose of this study we anticipate some of the initial costs presented in this section may already have been addressed by some establishments. It is therefore fair to conclude that the overall cost estimates provided in this RIAS overestimate the real costs related to these CTO Regulations as these costs may have already been incurred by these establishments in an effort to achieve compliance.

Methodology

A survey of the entire CTO Community population was used to quantify the incremental benefits and costs of implementing the standards. This methodology was seen as the most reliable given the fact that every identified establishment across Canada would be given an opportunity to state how they were following the standards and identify the area of potential financial burden for their establishment. It was also felt that establishments were in the best position to identify the gaps within their own facilities. The number and type of establishments surveyed in the study, as well as the response rate, is identified in Table 1.

To capture the varying information related to establishment type, six different questionnaires were developed based on the National Standards. The respondents were asked to identify their level of compliance with the requirements of the relevant standards and estimate the additional costs necessary to bridge the gaps in their compliance.

Table 1: Type and Number of Establishments and Response Rate to the Survey

<i>Type of Facility</i>	<i>Number of Establishments</i>	<i>Response Rate (%)</i>
Eye Banks	7	77.8
Tissue Banks	9	57.1
Bone Marrow Transplant Programs	15	53.3
Organ Donation Programs	15	73.3
Organ Transplant Programs	25	28
Stem Cell Laboratories	5	40
TOTAL	76	51.3

Compliance Level

Respondents answered questions regarding different sections of the National Standards. The overall results demonstrate a relatively high level of self-reported compliance with all standards across establishment types (See Table 2). Clearly, a higher level of compliance will diminish an establishment’s incremental cost of meeting the standards, and therefore the CTO Regulations. It is anticipated that since 2003, this compliance level has increased with the National Standards and Health Canada’s Directive and Guidance Document.

Table 2: Percentage of Compliance by Type of Establishment

<i>Compliance Level (%)</i>	<i>Not at all</i>	<i>Somewhat</i>	<i>Fully Compliant</i>
Eye Banks	4	7.4	88.6
Tissue Banks	1	6.3	92.6
Bone Marrow Transplant Programs	5.6	14	80.4
Organ Donation Programs	2.9	14.7	82.4
Organ Transplant Programs	5.4	8.5	86.1
Stem Cell Laboratories	3.7	18.1	78.2

Note : Totals for each establishment type equals 100%, representing all respondents in each category.

Estimated Costs

To determine the financial impacts, establishments were asked to quantify the gaps between their current practices and what the National Standards prescribe. Due to the relative size of the National Standards, it was deemed impossible to ask each establishment to cost each section of the standards. Therefore, cost estimates were provided in the following categories: Building, Testing, Personnel, Equipment, Computerization/Record Keeping/Reporting, and Other (which included a combination of activities like audits, training and developing SOP).

The costs were broken down according to these 6 different categories and were designated as initial (first year only) or ongoing costs (20 year period at a 5% discount rate) to recognize that some costs would be recurring and some would not. For example, hiring one staff would have cost implications for this year and upcoming years. On the other hand, adding building space would have cost implications for the construction year. The total costs (including initial costs) per establishment type and per cost category are shown in Table 3.

Table 3: Total (and Initial) Costs of Meeting the Standards by Type of Establishment and by Cost Category, ongoing costs discounted at 5%, all costs represented in millions of dollars.

	Buildings	Testing	Personnel	Equipment	Computers	Other	TOTAL
Eye Banks	0.03	1.81	4.45	0.25	0.05	0.04	6.63
<i>Initial Cost</i>	<i>0.03</i>	<i>0.21</i>	<i>0.33</i>	<i>0.17</i>	<i>0.03</i>	<i>0.04</i>	<i>0.8</i>
Tissue Banks	5.11	0.44	14.31	0.16	0.05	0	20.06
<i>Initial Cost</i>	<i>3.15</i>	<i>0</i>	<i>1.23</i>	<i>0.16</i>	<i>0.05</i>	<i>0</i>	<i>4.58</i>
Bone Marrow Transplant	0.75	0	8.26	3.8	0.47	0	13.28
<i>Initial Cost</i>	<i>0</i>	<i>0</i>	<i>0.78</i>	<i>1.45</i>	<i>0.1</i>	<i>0</i>	<i>2.33</i>
Organ Donation	4.2	6.12	20.34	0.22	0.44	0.34	31.66
<i>Initial Cost</i>	<i>0.48</i>	<i>0.45</i>	<i>1.77</i>	<i>0.17</i>	<i>0.34</i>	<i>0.03</i>	<i>3.24</i>
Organ Transplant	0	0	103.9	4.17	63.05	0	171.12
<i>Initial Cost</i>	<i>0</i>	<i>0</i>	<i>7.83</i>	<i>4.17</i>	<i>5.42</i>	<i>0</i>	<i>17.42</i>
Stem Cell Laboratories	0.19	0	1.2	0.32	0.13	0	1.83
<i>Initial Cost</i>	<i>0.16</i>	<i>0</i>	<i>0.17</i>	<i>0.32</i>	<i>0.13</i>	<i>0</i>	<i>0.78</i>
TOTAL	10.28	8.37	152.46	8.91	64.19	0.37	244.59

Note : Initial costs are included in the Total costs per establishment type and per cost category. Discounted ongoing costs can be determined by subtracting Initial costs from Total costs.

Benefits

The objective of introducing National Standards and regulations is to ensure all required procedures related to retrieval, processing, testing, labelling, storage and distribution of CTO for transplantation are met, to reduce the incidence of adverse reactions and errors and accidents in CTO recipients. Benefits from implementing the National Standards would accrue from:

- improved handling procedures in the period predating the implementation of the standards, resulting from establishments updating their infrastructure and staff in anticipation of the new standards;
- greater consistency in handling procedures that would result from the adoption and implementation of the National Standards across all establishments; and,
- reduced costs to healthcare institutions and individuals from fewer adverse medical reactions, shorter hospital stays, etc.

GGI's benefit-cost analysis demonstrated that the minimum level of benefits for meeting the requirements of the National Standards over the next 20 years (discounted at 5%) is estimated at over \$1 billion. This greatly exceeds the total costs estimated at \$244 million over the same time period, identified in Table 3.

Other Costs and Benefits to Establishments - Registration

In addition to adhering to the National Standards, some establishments, such as source establishments, distributors and importers, will be required to register with Health Canada and declare their compliance with the CTO Regulations. Although registration with Health Canada will be free of charge, minimal costs will be incurred by each registering establishment to prepare registration documentation. They will also have to attest to compliance with the regulations. From a trade perspective, distributors who import tissues could determine that the cost of registering does not justify remaining in this business. However, since registering with Health Canada has no attached fee, it is not anticipated that this will be an issue.

With regards to the benefits, registration of establishments will provide the regulator with a tool with which to act in the event of an infectious disease transmission. The registration will provide a known point of contact from which to trace all the affected CTO products for transplantation. Better record keeping and communication of errors, accidents and adverse reactions between all establishments will further benefit the system with improved traceability of product from donor to recipient. Therefore, the costs associated with registration activities will be outweighed by having a safer supply of CTO and will provide the regulator with a clear composition of the current Canadian industry.

Manufacturers of Medical Device Containing CTO

There is no immediate impact for manufacturers of CTO that are currently classified as Medical Devices (i.e. heart valves & dura mater) since for Phase I, they will continue to be regulated as Medical Devices. However, this advanced notice of Health Canada's intention to

regulate these products under the CTO Regulations in Phase II will give these manufacturers more time to adapt to this proposed change.

Donors and Donor Families

It is anticipated that donors and their families will not be financially affected by these regulations. However, donors and their families will benefit from increased confidence in a transplantation system that uses basic safety requirements for CTO formalized in regulations, with a long term potential of further increasing the number of donations of CTO. Requiring that CTO be handled in a safe manner emphasises the value donors place on the gift itself and reaffirms improved health benefits to the recipient.

Transplant Recipients

It is anticipated that recipients of transplanted CTO will not be financially affected by the CTO Regulations. Nevertheless, it is possible that some establishments will prefer to discontinue the distribution of CTO or that foreign CTO may be lost due to a supplier's decision not to register with Health Canada. This would ultimately reduce the supply of CTO available for transplantation in the short term, while the system adjusts in the long term.

However, the benefits of transplantation are significant for recipients. This includes the increased confidence that the transplanted CTO has met basic safety requirements in its processing and handling, thus greatly reducing the possibility of an adverse reaction such as the transmission of an infectious disease. Greater consistency in processing and handling procedures by all establishments will also increase the likelihood of a successful transplantation, and a healthy recovery for the patient.

Hospitals and Transplant Programs, Provincial and Territorial Governments

While hospitals and transplant establishments may require additional staff to fulfill the new requirements for record keeping, and error, accident and adverse reaction monitoring and reporting, they will benefit from the knowledge that the CTO products available are safer for therapeutic use. Having safer CTO products will result in fewer costs to these establishments related to follow-up and treatment of recipients.

Due to the nature of the system, it is anticipated that the provincial and territorial governments will be required to fund the gap between current practice in all establishments and the requirements prescribed in the regulations. However, provincial and territorial governments have called on Health Canada to develop this regulatory framework, have participated in the development of the National Standards and were informed of the release of the Directive and Guidance Document.

Provincial and territorial governments will benefit in the long term through reduced costs to establishments, healthcare institutions and individuals from fewer adverse medical events and

shorter hospital stays. These results of the benefit-cost analysis were circulated extensively among provincial/territorial governments and key stakeholders.

Public

The public will not pay a direct cost for the investments some establishments will be required to make in order to comply with the CTO Regulations. Potential recipients of CTO will benefit from the peace of mind of knowing that the safety of available CTO for transplantation is maximized by the regulations. Public confidence in the safety of transplantation procedures themselves may ultimately increase the number of those willing to become future CTO donors.

Evaluation

A two-staged comprehensive evaluation of the regulatory framework for CTO for transplantation is planned. A formative study to assess the extent to which the framework has been implemented as planned, and to identify areas for adjustment, will be conducted one year after implementation of the framework. A summative study of outcomes and objectives achieved will be carried out within five years of the formative study. In addition, ongoing monitoring will occur throughout the life cycle of the framework to provide Health Canada with information on the performance of the framework vis-à-vis intended objectives. This information will also be used to support the formative and summative evaluations.

Evaluation will address questions concerning: rationale and continuing need for the regulatory framework; whether the framework is being implemented as planned and is progressing towards achievement of intended outcomes; success in relation to intended outcomes; cost effectiveness relative to other potential design and delivery approaches; and lessons learned for the future. In addition to assessing the extent to which the framework has made progress towards maximizing the safety and quality of CTO for transplantation, evaluation will assess whether the standards-based approach to regulation is working as intended.

Consultation

Over the past decade, stakeholders have been given the opportunity to provide input on these developing regulations through a series of public consultations and communication activities across Canada. In November 1986, the Health Services and Promotion Branch of Health Canada published *Guidelines for Establishing Standards for Special Services in Hospitals - Organ and Tissue Donation Services in Hospitals*. This was one of the first comprehensive documents to emphasize the importance of minimizing the risk of disease transmission through CTO transplantation.

One of the first external reports to recommend regulatory intervention by Health Canada, published in December 1994, was entitled "Safety of Human Organ and Tissue Transplantation in Canada". The working group for this report was assembled through Organ Sharing Canada, which was established in 1992 by a joint initiative of the executives of the Canadian Association of Transplantation and the Canadian Transplantation Society. Among the recommendations

made were that “National Standards for organs and tissue transplantation be established, that a process be developed for the mandatory certification and accreditation of all organ and tissue transplant programs and that the standards established by a national agency be used for accreditation and inspection programs”.

On October 29-31, 1995, Health Canada sponsored the National Consensus Conference on the Safety of Organs and Tissues for Transplantation. Participating stakeholders included representatives from the Canadian Red Cross Society, the Canadian Organ Replacement Registry, Québec-Transplant, the Eye Bank of Canada, the Ontario Ministry of Health, the Canadian Transplant Society and the British Columbia Transplant Society. These participants proposed that the Canadian General Standard on Safety of Organs and Tissues for transplantation be revised to incorporate input from experts at the conference (this standard was the very first draft version of what would become the National Standard). They further recommended that the revised Canadian General Standard on Safety on Organ and Tissues for Transplantation be accepted as a template for the development of subsets of specific standards for individual organ and tissue types. Both these recommendations have been incorporated in the development of the National Standards.

In September 1996, the interprovincial working group created by the Advisory Committee on Health Services (ACHS) produced a report entitled “Organ and Tissue Donation and Distribution in Canada: A Discussion Document”. This early consultation with the provinces produced a resounding support for Health Canada’s initiatives in the development of National Standards for donor screening, serological testing, record-keeping, packaging and labelling and storage, including the safety aspects of laboratory testing and transportation.

In April 1999, the report entitled “Organ and Tissue Donation and Transplantation: A Canadian Approach” was published by the House of Commons Standing Committee on Health. The Committee gave all stakeholders and the general public an opportunity to express their views on CTO. To achieve this, the Committee held public hearings over the course of two months, during which it heard from over 100 individuals. In addition, it accepted written briefs from other individuals and organizations. The Committee recommended that the Minister of Health ensure that the Canadian General Standard for Safety of Organs and Tissues for Transplantation and its subsets be approved and made mandatory through incorporation by reference into regulations made under the F&DA as soon as possible.

A report entitled “A Coordinated and Comprehensive Donation and Transplantation Strategy for Canada” was published in November 1999 by the National Coordinating Committee (NCC) for Organ and Tissue Donation, Distribution and Transplantation for the Federal / Provincial / Territorial Advisory Committee on Health Services (ACHS). The Committee recommended that “the safety standards for perfusable organs, ocular and other tissues, sperm, bone marrow and xenotransplantation be referenced in the F&DA”, thus making them mandatory.

In November 2001, Health Canada published an Information Kit entitled “Towards Renewed Regulatory Frameworks for Whole Blood and Blood Components Intended for Transfusion and Cells, Tissues and Organs Intended for Transplantation and Assisted Reproduction” (Info Kit).

In the Info Kit, Health Canada clearly detailed its proposals for new CTO Regulations under the F&DA. It stated that the proposed regulations would be based on the safety requirements listed in the National Standards, and that other key elements of the regulatory framework would include surveillance and adverse reaction reporting, and a compliance monitoring and enforcement strategy.

The Info Kit also explained that the CSA's process for developing National Standards requires public review of the standards. To fulfill this requirement, copies of the draft Standards were sent to provincial/territorial representatives, CTO programs and all individuals who had expressed a desire to comment on the draft. The over 1,000 comments received through the public review process were referred to the CSA Technical Committee for consideration. The National Standards have now met the requirements of the Standards Council of Canada. Namely, they were drafted through a consensus-development process, and an extensive opportunity for Canadians to express their opinions or concerns about these new National Standards has also been afforded.

The Info Kit has been updated and re-printed twice (in 2003 and 2004) in order to update the community with information regarding the regulatory framework for CTO. The Kit has been sent to all known establishments and individuals that handle and/or process CTO for transplantation, providing information on the progress of the developmental process, as well as inviting stakeholders to the many consultations and public information sessions offered over that same period. The extensive public consultation process on the new National Standards offered an opportunity for Canadians to express their opinions or concerns and was considered sufficient to move forward with regulations.

A series of one-on-one meetings with provincial/territorial representatives have provided periodic progress reports on the developing CTO Regulations and solicited feedback and collaboration in areas of overlapping jurisdiction, with a view to maximizing the safety of Canadian transplant recipients. Presentations on the CTO regulatory framework made to the Canadian Council for Donation and Transplantation (CCDT), which includes representation from the provinces and territories, has further ensured the provinces' awareness of the requirements and impact of the regulations. In addition, the results of the benefit-cost analysis of the National Standards conducted by Goss Gilroy Inc in 2003 were circulated extensively among provincial/territorial governments and other key stakeholders. Consultations were held in October 2005 with provincial and territorial representatives to examine compliance monitoring and enforcement and error, accident and adverse reaction reporting options for Phase II, which provided yet another opportunity to update our partners on the CTO Regulations.

Since 2001, Health Canada has further promoted the creation of the regulatory framework for CTO by making several (greater than 60) presentations to professional associations, and provincial governments. Stakeholder input on the more comprehensive adverse reaction reporting and compliance monitoring and enforcement options for Phase II of the CTO Regulations was initiated with four regional consultations in March 2005, held in Toronto, Edmonton, Halifax and Montreal. The feedback obtained from those consultations will be

considered in the development of the Phase II Regulations, and the final report has been posted on the Health Canada web site.

In summary, the consultation mechanisms employed in the creation of the regulations have permitted extensive opportunity for stakeholder feedback. During the consultations, no group or association expressed concerns about the new standards-based regulations. In fact, as shown above, Health Canada has reacted to the needs expressed by the CTO community by initiating the regulatory process to maximize the safety of products for transplantation across Canada. As the development of the regulatory framework continues, Health Canada continues to communicate, both in writing and in face-to-face meetings, with provincial/territorial governments to discuss the impact of the CTO Regulations on their jurisdictions.

The CTO Regulations were pre-published in *Canada Gazette*, Part I on December 10, 2005. At that time, CTO programs identified in the National Review; the pharmaceutical industry and associations, Deans and Registrars of Pharmacy, Medicine and Dentistry, Provincial and Territorial Ministries of Health, professional associations of physicians and dentists, hospitals and other CTO stakeholders were notified of the publication and informed of the 75-day comment period that followed the publication.

In response to the 75-day comment period, Health Canada received questions of clarification from fifteen organizations including: transplant programs (5); provincial/territorial governments (2); dental associations (1); tissue banks (1); organ donation organizations (1); professional associations (1); laboratories (1); and unknown sources (3).

In addition to the requests for clarification, Health Canada also received sets of comments and recommendations from thirty-two (32) organizations: provincial/territorial governments (2); dental associations (1); transplant programs (8); tissue banks (6); lymphohematopoietic transplant programs (6); organ donation organizations (2); professional associations (2); public cord blood banks (1); and four (4) foreign organizations including, tissue banks (1), professional associations (2) and governments (1).

Comments and recommendations received during, and after the close of, the 75-day comment period were crucial in the further development of these regulations. Changes have been made to the regulations that are direct results of stakeholder input. While the safety of CTO as well as health considerations remained our primary focus, these changes resulted in less stringent requirements for CTO establishments. Comments resulting in changes to the regulations, as well as comments not incorporated into the regulatory framework, and the responses to same are outlined below.

Comments (C)/Responses (R):

Interpretation

C: The language used in the regulations to describe activities and organizations are not commonly used in the donation and transplantation community.

R: Health Canada recognizes that some of the terminology and language used in the regulations has not been commonly used in the CTO community to this point. However, because the regulations apply to diverse CTO and many different types of establishments, terminology and language that could encompass and accommodate all CTO and establishments was needed. In addition, there are constraints on the use of language in the context of legal text, such as regulations, that must be taken into account. For these reasons, language familiar to the CTO community was not always suitable for use in the regulations; however, commonly understood language is employed when possible.

C: The exemption of the retrieval of organs in the definition of processing is not fully understood.

R: Organ retrieval is a surgical procedure carried out in a manner that is adapted to the donor organ and the needs of the recipient, and thus considered to be within the domain of medical practice. As Health Canada does not regulate medical practice, the retrieval of organs is exempt from the definition of processing and related requirements under the regulations.

Application

C: The scope of Phase I CTO regulations does not include lymphohematopoietic cells for autologous use.

R: The primary objective of Phase I of the regulations is to maximize the safety of CTO by addressing safety requirements in the processing and handling of CTO for transplantation, with an emphasis on donor screening and testing for transmissible disease, and linking the CTO donor to the recipient. Health Canada acknowledges that there are safety concerns around the autologous use of lymphohematopoietic cells. However, these safety concerns are not related to the suitability assessment of the donor, the transmission of disease or linking the donor to the recipient. For this reason, lymphohematopoietic cells for autologous use were not included in Phase I of the CTO regulations; however, because of the potential safety issues around these products, Health Canada may consider including lymphohematopoietic cells for autologous use in the scope of the regulations for Phase II.

C: It is unclear as to why islet cells are not included in the scope of the regulations.

R: The classification of islet cells has been revisited and Health Canada has determined that they will be classified as a minimally manipulated CTO. Appropriately, changes to the regulations have been made.

C: It is unclear how the regulations address adjunct vessels that are retrieved with organs and used in organ transplantation.

R: Unlike banked tissue, these vessels are either used at the time the organ is transplanted or can be stored and used up to three days after they are retrieved, if an organ recipient runs into

difficulty. This time frame does not allow for all the regulatory requirements for tissue testing to be met. Therefore, it would be necessary to apply the exceptional distribution provisions in every case were these vessels were needed. Health Canada has determined that these vessels must meet the regulatory requirements pertaining to organs. Guidance will be issued regarding storage of these vessels at the transplant establishment.

Registration

C: It is unclear how establishments will know the registration status of other establishments, for example, which establishments are registered, had their registration cancelled.

R: Health Canada currently posts a list of those holding establishment licenses on its website. If a name does not appear on the list of license holders, parties can contact Health Canada to enquire as to whether a license has been issued. The scheme established by the CTO Regulations uses a registration scheme. It is expected that Health Canada will post a list of those establishments holding a registration under the new regulations. Public disclosure of the names of successful registrants is consistent with the overall purpose of the CTO regulatory framework and is necessarily incidental to compliance with the various regulatory obligations under the scheme. Although Health Canada does not currently post a list of licenses that have been suspended, canceled or revoked, the ability to do so is being explored.

C: The consequences of a medical director signing an attestation of compliance if the establishment is subsequently found to be non-compliant with the regulations are not clear.

R: The appropriate response to this scenario very much depends upon the actual facts and relates to two contexts. The first context relates to the time at which the application is made. To comply with the regulatory requirements in the CTO regulations, the medical director must have the requisite legal authority to make the attestation on behalf of the establishment. A medical director who did so, knowing that he or she did not have such authority, would be acting in contravention of the regulations and could be charged with an offence. A medical director who had the legal authority to make the attestation but was not duly diligent in ensuring that the establishment was compliant with the regulations (e.g. did not make the inquiries that a reasonable person would have made in similar circumstances) could also be charged with a regulatory offence. A medical director who acted in good faith, and was duly diligent in examining all facts that are reasonably considered relevant to an assessment of compliance will likely not be subject to a regulatory offence if a subsequent non-compliance finding is made.

The second context pertains to findings of non-compliance after the application for registration has been made. There is a regulatory requirement that the establishment must advise the Minister of Health in writing of any change in the information provided in the application for registration. The latter would include changes in procedure or facts that affect compliance with the regulations. It is anticipated that, as in the past, Health Canada will work with the establishment involved to help it come into compliance with the regulations.

C: The regulations do not require foreign lymphohematopoietic donor centres to register. However, the regulations prohibit importation of CTO unless the foreign establishment is registered with Health Canada. This creates a Catch-22 situation in which the importation of lymphohematopoietic cells is made impossible. Since Canada is heavily reliant on lymphohematopoietic cells from foreign donor sources, this has a significant negative impact on Canadian access to life saving transplants.

R: There was an error in the regulations, it was never Health Canada's intent to prohibit importation from foreign lymphohematopoietic donor centres. The intent of this provision of the regulations was to ensure that all foreign SOURCE establishments register with Health Canada. The regulations have been modified such that it is now only prohibited to import from source establishments that are not registered. This addresses the supply problem because the source establishment for lymphohematopoietic cells is the Canadian transplant establishment, there are no foreign source establishments for lymphohematopoietic cells. Additionally, section 4(2) under "Prohibition", has been amended to allow establishments to import lymphohematopoietic cells from establishments that are not registered with Health Canada.

C: The rights of establishments, as well as the appeal/adjudication process, are not clearly stated.

R: While the CTO Regulations do not create a statutory right of appeal, decisions made by the Minister must comply with the Regulations and respect the principles of administrative law. Establishments will be able to challenge regulatory decisions by way of judicial review. This process will be explained in the Registration Guidance Document.

Processing

C: For lymphohematopoietic cells that are the subject of an importation, it is impossible for Canadian establishments to obtain all of the donor screening information needed in order to comply with the regulations.

R: The regulations have been modified so that Canadian establishments that import lymphohematopoietic cells will be able to assess the suitability of the donor with the donor screening information they are able to obtain from the foreign establishment.

C: It is unclear why the CTO regulations allow pooling under certain circumstances, while the CSA standards prohibit it.

R: Pooling of CTO is permitted in the regulations, even though section 15.5.1 of the CSA general standard states that 'cells, tissues, and organs from donors shall not be pooled during retrieval, processing, preservation, or storage'. The reason for the difference is that, in the CTO regulations, CTO from multiple donors may be pooled in order to facilitate the treatment of a single recipient where the CTO obtained from one donor may not suffice. Two examples where the ability to pool CTO to obtain a therapeutic dose is important to the success of the procedure are in the cases of lymphohematopoietic and islet cell transplantation.

C: The regulatory requirement that all CTO donor specimens be tested for infectious diseases using test kits specifically licensed for screening donors will represent an important challenge for Canadian CTO establishments.

R: It is scientifically recognized that donor screening test kits are more sensitive when compared to diagnostic test kits, and are therefore considered safer. International standards, including the United States Food and Drug Administration and the European Union, require tests that are licensed for screening donors. In the case of organs, Health Canada agrees that tests licensed for the screening of donors may not be accessible in the time frame necessary to retrieve and transplant organs. Therefore, in the case of tests performed on organ donor specimens, the regulations have been modified accordingly. However, in the case of cells and tissues, the test kits will have to be licensed for screening donors. Health Canada recognizes that some cells and tissues establishments may need time to evaluate their options and comply with this requirement; a transitional period will therefore be granted.

C: It is unclear why human leukocyte antigen (HLA) testing is not a requirement in the donor screening section of the regulations while the CSA standards do require it.

R: Health Canada's regulatory authority lies in the safety of products pursuant to the *Food and Drugs Act*, the enabling legislation for the CTO regulations. While HLA typing may be clinically beneficial in some circumstances, and thus is an issue in determining the suitability of an organ for a recipient, it is not necessarily related to the safety of the organ as a product. For this reason, HLA typing is not required for organ donors under the regulations.

C: It is unclear why testing for West Nile Virus (WNV) is not a requirement in the CTO regulations.

R: The transmissible disease testing requirements in the CTO regulations are based on sections of the CSA standards, and its organ and tissue specific subset standards, have been referenced in the regulations. The required tests depend on the CTO in question, and are determined by the CSA through extensive collaboration with experts in each respective field. In this way, the standards, and in turn the regulations, are responsive to advances or changes in transmissible disease testing practice. The CSA does not suggest WNV testing as a matter of course in the general, or the subset, standards. In addition, there are currently no licensed kits available in Canada for WNV testing of deceased donors. For these reasons, Health Canada cannot make WNV testing a regulatory requirement. However, the CTO Regulations stipulate that the establishment's donor screening questionnaire must include questions relating to WNV symptoms.

Exceptional Distribution

C: Requiring the medical director's approval on all exceptional distributions is problematic.

R: The requirement to have medical director approve every exceptional distribution has been removed. A source establishment may now distribute CTO under the exceptional distribution

clause that have not been processed in accordance with these regulations, provided that the transplant physician or dentist authorizes the distribution. In addition, the recipient must have given his/her informed consent.

C: The regulations prohibit the importation of lymphohematopoietic cells unless they are processed by a registered establishment. Maintaining this requirement would effectively make it impossible to access lymphohematopoietic cells from foreign sources.

R: A Canadian establishment may now import lymphohematopoietic cells from establishments that are not registered with Health Canada.

C: It is not a requirement in the regulations for foreign source establishments for organs to be registered with Health Canada. Therefore, the sole mechanism for accessing organs from foreign sources is the exceptional distribution mechanism. If the only reason for the exceptional distribution of an organ is because it originated at a foreign establishment, in some high-profile incidences, the confidentiality of the donor may be compromised. For this reason, combined with the reality of the relatively high volume of imported organs used in Canadian transplants, the use of exceptional distribution as the only mechanism for accessing organs from foreign sources is not feasible.

R: The regulations have been modified so that organs from foreign sources may be imported into Canada without having to comply with the exceptional distribution provisions.

Records

C: Maintaining the requirement to keep certain records indefinitely will most likely lead to a Canadian supply shortage as foreign sources are not required to keep records for that length of time.

R: The regulations have been changed to require that all records must be kept for a minimum of 10 years after the date of transplantation or final disposition, whichever is latest. Health Canada will revisit this decision at a future date to determine if this requirement will remain.

Quality Assurance System

C.: It is unclear if an establishment is required to have separate standard operating procedures (SOP) for requirements that fall under provincial/territorial versus federal jurisdiction.

R: Establishments are not required to have separate SOP for requirements that fall under both federal and provincial/territorial jurisdiction in view of the expectation that inspectors can clearly distinguish which activities are under federal jurisdiction. The matter will be addressed in Phase 2 if any problems arise in this regard.

C: The audit process is not understood.

R: The process related to audits will be explained in a guidance document. This guidance will further explain when and how establishments are to conduct audits to verify compliance with the regulations and SOPs. For example, the guidance will provide that the audit may be done by individuals working in the same establishment, but only if they are not directly involved in the activities being monitored. It will state that personnel conducting audits must be knowledgeable in the subject matter and process being audited, and that there must be defined responsibilities for the audit activity.

Powers of Inspectors

C: There is concern regarding access of inspectors to confidential medical information.

R: Health Canada is responsible for the fair, consistent and uniform application and enforcement of the *Food and Drugs Act* and its associated *Regulations* for all products under the mandate of the Health Products and Food Branch. To fulfill this responsibility in respect of the CTO Regulations, this may mean that an inspector will access files in an establishment which contain confidential medical data.

Where the confidential medical data is in respect of an identifiable individual, the collection and disclosure of such information must be consistent with the *Personal Information Protection and Electronic Documents Act* and with the federal *Privacy Act*. The confidential medical information can be shared with inspectors appointed pursuant to the *Food and Drugs Act*. However, the disclosure and use of the information by Health Canada must be in accordance with the *Privacy Act*. For example, the personal information may be disclosed to inspectors and used by them for the purpose of ensuring compliance with the CTO regulations.

Transitional Provisions

C: It is not understood why there is a need for transitional provisions in the CTO Regulations.

R: Analysis of the current situation has resulted in the review of the Transitional Provisions. They now require that cells and tissues that were processed within five years before the regulations are registered can only be imported and/or distributed by a registered establishment. CTO processed prior to the coming into force of the CTO Regulations must meet certain safety requirements, namely that every registered and transplant establishment must ensure that the donor identification code is a component of its record system, and that all establishment's records must contain information with respect to all CTO that it processes, distributes, imports or transplants that identifies both the establishment from which it received the CTO, and all establishments to which it will be distributed. These provisions will remain in effect for five years.

Furthermore, Health Canada will continue to exercise its authority under Sections 8 and 19 of the *Food and Drugs Act* to prohibit the distribution of products that 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.

Compliance and Enforcement

The compliance monitoring and enforcement scheme that accompanies the CTO Regulations provides Health Canada with a means of staying abreast of existing CTO establishments, the types of CTO being processed, the activities in which they are engaged, and their level of compliance with the regulations. Establishment registration will provide Health Canada with information that can be used to assess the risks associated with establishments' activities related to the handling/processing of CTO, as well as provide an enabling mechanism to assess compliance.

Prior to the enactment of the CTO Regulations, compliance will continue to be monitored through the ongoing National Review of establishments handling and/or processing CTO for transplantation. In the interim, establishments must adhere to the basic safety requirements specified in Health Canada's Directive and Guidance Document.

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