

Overarching Observations

- There appears to be confusion between the issue of the safety of tissues used in transplantation and its link to the current structure of the administration of health care in Canadian provinces and territories, as it relates to tissue banking :
 - Criticisms of organizational structure do not mean that unsafe tissue being distributed in Canada for use in transplantation.
 - Differences in tissue banking systems do not mean that tissue distributed in Canada for use in transplantation is unsafe.
- The terms safety and quality are two distinct terms in relation to transplanted tissues, but this distinction is not made evident in the current Canadian context;
- Gaps pertaining to the current safety of tissues used in Canada are not identified, rather the analysis pertaining to safety involves conjectures based on past incidents, absent of the past Canadian context, and assumptions that do not reflect the current state of tissue safety in Canada;
- There is a general lack of evidence to support statements and there are often assumptions made in the analysis that are not demonstrated and do not reflect either the current context within Canada or what Health Canada has observed through its inspections of cell, tissue and organ (CTO) establishments.

Section Specific

Introduction

- This document is intended “to identify and explain elements of the OTDT system in order to improve patient outcomes” however a key element, the distinct roles of federal, provincial and territorial governments has not been addressed.
- The CfC does not recognize positive impacts from any of the undertakings intended to bolster the safety of tissues used in transplantation in Canada, including:
 - The publication and maintenance of national standards for CTO safety;
 - The implementation of the *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* (CTO Regulations);
 - The initiation of federal inspections to enforce compliance to the CTO Regulations.

Section 1

We feel that the statement “because of the fragmented nature of the tissue bank system in Canada, there exists an underlying set of gaps that undermine patient safety and product quality and system efficiency.” is not justified:

- Although tissue establishments may differ in their organizational structure, all tissue banks that process, import or distribute human tissue for use in transplantation in Canada are required to comply with the safety standards established of the CTO Regulations;
- The CTO Regulations have established mandatory minimum safety requirements for CTOs used in transplantation in Canada in order to bolster the safety of these therapeutic products and to mitigate the risk of infectious disease transmission from the transplanted CTO to the transplant recipient;
- The CfC discusses the establishment of the CTO Regulations and then states: “there are many gaps in the safety and quality frameworks of individual tissue programs and facilities that transplant tissue.” This implies that there are gaps in the CTO Regulations with the result that tissue safety is being compromised, yet no specific gaps are identified.

Re: Subsection 1.1

We feel it is misleading to say that “there is inconsistent application of standards, regulations, and leading practices in Canadian tissue banks, resulting in inconsistent quality and safety of tissue products.”

- Regulations are mandatory requirements that hold the force of law. Industry standards/professional leading practices are voluntary for industry unless incorporated by reference into law.
- The CTO Regulations came into force in December 2007, with exception of Subsection 26(1) which came into force in June 2008. The CTO Regulations incorporate by reference portions of the CSA Z900 series of standards and the incorporated standards have the force of law.
- Health Canada established a Guidance Document in order to assist CTO establishments in their implementation of the requirements of the CTO Regulations to ensure consistency in regulatory interpretation. Included in this Guidance Document is contact information, so that tissue banks and other CTO establishments can contact Health Canada if they have questions on the regulatory requirements or the intent behind them.
- The Regulations are being consistently applied to tissue banks that process or handle human tissue for use in transplantation in Canada.
- Since the summer of 2009 Health Canada has been inspecting CTO establishments, including tissue banks, for compliance against the CTO Regulations. Health Canada has seen through these inspections that tissue banks are applying these regulations in a consistent manner.

In regards to the analysis on the implementation of recommendations:

- Recommendations by either standards associations or by Health Canada are not mandatory requirements and therefore do not have to be implemented by establishments;

- Similar to the World Health Organization, Health Canada recommends NAT testing for West Nile Virus and the other viruses listed in the examples of this section of the CfC. **NAT testing was not made a mandatory requirement in the CTO regulations based on the CTO community's identification that this test was not available in all regions of Canada and that requiring such a test would likely result in the shutdown of key CTO related establishments, as they would be unable to screen and test donors as required by regulation.**

In terms of limited ability to respond to emerging issues and safety incidents:

- The framework of the CTO Regulations was structured in order to enable quick responses to emerging issues and safety incidents. The CTO Regulations incorporate by reference CSA Standards that can be amended through the submission of a Proposal for Change. In fact, numerous amendments to the Standards have been made since its publication in 2003 and the second version of the Standard will be released later this year, updating the requirements and incorporating the most recent proposals for change;
- Health Canada continually dialogues with the CTO community on both emerging issues and safety incidents;
- In 2009, one year following the implementation of the regulations, Health Canada held a series of follow-up information sessions with CTO stakeholders. The purpose of these CTO Information Sessions was to provide CTO establishments with an opportunity to gain a better understanding of the regulatory requirements under the CTO Regulations including how emerging issues were being addressed. The Information Sessions were organized to inform and educate CTO establishments on the safety requirements, and to provide them a way with an opportunity to interact directly with Health Canada and other CTO establishments. Health Canada invited 135 registered CTO establishments, as well as representatives from professional association and provincial governments to the CTO information sessions, which were held across Canada in the cities of Halifax, Montréal, Toronto, Winnipeg, Saskatoon, Edmonton and Vancouver, between the dates of January 25th, 2009 and February 12th, 2009. In an effort to promote transparency and to maximize access to the information sessions and reach as many stakeholders as possible, teleconferencing, videoconferencing and web-casting was made available, where possible, for establishments who indicated that they wished to participate but could not attend in person. A total of 251 people registered for the information sessions, including those who attended by remote access;
- Health Canada has established and engages the Expert Advisory Committee for CTO, an external committee of experts in the field of CTO transplantation and donation, to consult with on current and emerging issues;
- Health Canada has issued fact sheets and notices to CTO establishments and the broader CTO community as appropriate, including during the recent influenza pandemic. The quantity of these documents is not an indicator of Health Canada's responsiveness to emerging issues or incidents as such documents are issued based on both the need and scope of particular issues that emerge;

- In terms of safety incidents, the CTO Regulations have mandatory investigation and reporting requirements for errors, accidents and adverse reactions.

In terms of “lack of adoption of leading practices”:

- national standards can span areas that fall within both federal and provincial jurisdiction. Health Canada cannot regulate beyond its federal authorities and therefore cannot regulate activities within the delivery of health care or the scope of medical practice;
- The CTO Regulations are a comprehensive set of regulations establishing the minimum safety requirements for CTOs intended for use in transplantation in Canada. To provide rigid, detailed, prescriptive requirements to all CTO establishments would ignore the distinctive roles that each establishment fulfils during CTO donation processes. Regulating in such a manner would likely have resulted in substantial regulatory burden to some establishment, to the extent that they could no longer process or handle CTO within their respective provincial health care systems;
- Health Canada has developed a 106 page Guidance Document to provide greater clarity on the intent and the requirements of the CTO Regulations in order to assist CTO establishments. A draft version of this document was publicly consulted on and the comments received are reflected in the final April 2009 document. This document is intended to be updated and amended from time to time, in consultation with the CTO Community.

Re: Subsection 1.2

- Health Canada agrees that in order to manage the safety risks of human tissues intended for use in transplantation, that these products must be followed along their chain of distribution, including when there is a processing error or in cases when there is an adverse reaction in transplant recipients. However Health Canada strongly disagrees with the statement “In Canada, there is currently no comprehensive system to ensure complete traceability.”
 - The CTO Regulations establish labelling and record keeping requirements to enable tissues to be identified throughout their chain of distribution (from donor to recipient).
 - The CTO Regulations contain quarantining, reporting, and investigation requirements in the event that an error, accident or adverse reaction is detected. Further to this, the CTO Regulations contain requirements for establishments to have quality assurance systems in place.
 - Transplant establishments are required to keep information that allows the identification of the recipient as well as the donor identification number. This information can then be shared with source establishments, who are responsible for the processing and initial distribution of CTO, including tissue banks, in the event that an investigation is initiated and it is requested by the source establishment.

Further to this, in terms of information sharing:

- The CTO Regulations establish a comprehensive safety system for CTOs in which, during the course of an investigation, information can be shared between establishments. Section 50 of the Regulations states “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.”
- In terms of obtaining informed consent for transplantation procedures, that is a matter to be commented on by the provincial and territorial governments that administer health care. However, under the CTO Regulations, informed consent is consistently required if a cell, tissue or organ is exceptionally distributed.

Re: Subsection 1.3

The CTO Regulations contain mandatory investigation and reporting requirements for adverse reactions caused or suspected of being caused by the transplanted CTO. Adverse Reactions are to be reported to Health Canada’s Marketed Health Products Directorate, under its Canada Vigilance initiative.

- Guidance on how to report an adverse reaction, including contact information, where to access reporting forms, etc. is found in the *Guidance Document for Cells, Tissue and Organ Establishments: Safety of Human Cells, Tissues and Organs for Transplantation*.

Re: Subsection 1.4

- The examples of a safety incidents referred to in this section involved acts of intentional circumvention of existing laws and regulations, both in Canada and the United States, **prior** to the establishment of the CTO Regulations.
- Canada’s quick response to the cited cases, which included the identification of implicated tissues banked and/or distributed in Canada and the ceasing of the distribution of banked tissues that was imported from the implicated establishments, was not mentioned, which we believe gives the misleading impression that no capacity existed to take action to protect the safety of recipients and potential recipients of this tissue. In fact swift, effective action, with Health Canada and the provincial and territorial governments working closely and effectively together was taken in these cases.
- The CTO Regulations establish safety requirements, as well as compliance and enforcement measures, which further enhanced the safety of CTO that are imported into Canada for transplantation. This includes specific requirements for establishments that import tissues. No establishment can import tissue into Canada unless it is processed by a registered establishment under the CTO Regulations and determined safe for transplantation.

- Since the coming into force of the CTO Regulations, there have been no reported cases of infectious disease transmission in Canada as a result of a transplanted human tissue.
- Further to this, Health Canada's Health Products and Food Branch has a memorandum of understanding with the US Food and Drug Administration which is used facilitate information sharing regarding adverse reactions in instances that may involve imported cells, tissues or organs used in transplantation.
- We feel that the last paragraph of this section, referring to accreditation, FDA registration and the lack of auditing or inspection of foreign manufacturers is misleading. AATB and EBAA accreditation are voluntary accreditation programs and differ from what is legally required by establishments. Federal regulations are established in recognition of various considerations, which are not necessarily considered by accreditation programs. Furthermore, Health Canada has never indicated any intention to inspect foreign manufacturers, as our close collaboration with our international regulatory partners allows us to rely on their inspection programs of the establishments within their jurisdictions. For example, our Memorandum of Understanding with the US FDA provides us with access to inspection reports of US tissue establishments.

Re: Subsection 1.5

- A CTO surveillance system is under development and once in place should further enhance Canada's biovigilance capabilities.
- Along with the clinical trials required for products that are drugs or biologics, products which contain human tissue components that are considered to be medical devices require investigational studies to evaluate their claims, effects, etc., prior to being introduced into the Canadian market place. New tissue products containing, for example, more than minimally manipulated human tissue will have to go through these processes.
- The CTO Regulations apply to minimally manipulated tissues that have an established history of effectiveness of treatment based on years of transplantation in Canada and for which the medical outcomes have been well documented.

Section 2

Re: Subsection 2.1.

- Health Canada disagrees with the implied assumption that because a tissue is imported into Canada it must be considered inherently unsafe.
- In terms of safety, as noted under Subsection 1.4, the "safety incidents" involving imported tissue involved the intentional circumvention of existing laws in the United States and in Canada and occurred prior to the implementation of the CTO Regulations. These incidents do not reflect the current regulatory environment that exists in Canada which contains mandatory safety standards for imported human tissue used or intended for use in transplantation in Canada.

- In addition to needing to comply with the CTO Regulations if exporting to Canada, tissue establishments in the US are strictly regulated by the US FDA, with which Health Canada has a close, collaborative relationship.

Section 3

Re: Subsection 3.1

- Health Canada recognizes that the tissue banking system in Canada differs from that in the United States, as a result of differences in populations and country histories. It cannot be assumed that these differences in tissue banking systems result in negative consequences to the safety of tissues that are imported and banked in Canada for use in transplantation.
- Under the CTO Regulations, imported tissue must meet the safety requirements as that of tissue which is retrieved within Canada. Further to this, there are specific packaging and storage requirements that apply to imported tissue to maintain its integrity during the importation process, specifically:
 - Section 28 of the CTO Regulations requires that “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.
 - Section 37 of the CTO Regulations requires that “an establishment that ships cells, tissues or organs must ensure that they are stored during transportation in appropriate environmental conditions.”
- The analysis of Subsection 3.1 of the CfC does not take into account the current regulatory environment in Canada, or provide the historical context as to why the Canadian tissue banking system was established as it was, or indicate specific gaps in the tissue banking system in Canada.
- We find the section describing the “manufacturing model” used in the US confusing. The fact that the US system model is presented as something to aspire to seems to be directly contradictory to the allegations in Section 2 that our reliance on US tissue is presenting safety risks to Canadians. Furthermore the US model is presented only in a positive light, without identifying any of the drawbacks or negative aspects of such a system (e.g. The commercial aspect of tissue banking in the US is clearly one of the factors which resulted in the BTS incident where tissue was illegally procured in order to be sold).

Re: Subsection 4.1

Health Canada disagrees with the statement “There is no incentive or requirement for tissue banks to share information”.

- The CTO Regulations contain requirements for tissue banks to share information, and to specifically share information when there are suspected errors, accidents and adverse reactions concerning tissues that it distributed. [example: Section 50]
- During Health Canada’s engagement throughout the development of the CTO Regulations and after their implementation tissue banks have articulated and

demonstrated the desire to bolster the safety of the tissues that they distribute in order to mitigate the risks to transplant recipients. The sharing of information along the chain of distribution was identified as a key method to achieve this goal.