

Canadian Blood
Services

TISSUE EXPERT COMMITTEE: HOW CAN THE CANADIAN TISSUE SYSTEM BEST ENSURE CONSISTENT SAFETY AND QUALITY? (DRAFT SOLUTION DESIGN PAPER)

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1. Scope

HOW CAN THE CANADIAN TISSUE SYSTEM BEST ENSURE CONSISTENT SAFETY AND QUALITY?

This question seeks to evaluate the options available within tissue system to improve the current level of safety and quality. This package will explore the current regulatory framework and regulatory oversight in place for tissues as well as the application of quality assurance activities within the tissue donation and transplantation process. The package will reference audit, accreditation, and surveillance and traceability to provide insight into the overall quality and safety of tissue and the use of tissue. This paper will not address system improvements to traceability as this topic will be addressed by the solution design question focusing on traceability.

2. Current State

A. Current State

The quality and safety of tissue can be impacted by practices within each component of the donation and transplantation processes. This section will review the regulatory framework for tissues and the management of safety and quality in the Canadian tissue system.

Regulatory Framework for Tissues

Health Canada regulates biologics, including cells, tissues and organs, with the objective of assuring that biologics available to Canadians are safe, effective and of high quality. The *Safety of Human Cells, Tissues and Organs for Transplantation Regulations*¹ (CTOs) and the *Medical Devices Regulations*² (MDRs) impose minimum safety standards for the use of cells, tissues and organs, and medical devices. The CTOs apply to organs and minimally manipulated cells and tissues. If cells or tissues are more than minimally manipulated (e.g., demineralized bone products that contain handling components, or wound coverings containing human cells), they are considered medical devices and are regulated under the MDRs.

Prior to the implementation of the CTOs in 2007, a National Review undertaken by Health Canada demonstrated the need for regulatory oversight. The review discovered that some establishments were challenged in meeting basic safety requirements, specifically in the area of donor screening.³ The CTOs mandate specific practices in each component of the donation and transplantation process to establish minimum safety standards. The standards require establishments that distribute cells, tissues or organs to implement and maintain a quality assurance system. The CTOs incorporate, by reference, specific sections of the Canadian Standards Associations (CSA) standards related to tissue (CAN/CSA-Z900.1⁴, Z900.2.2-03⁵ and CAN/CSA Z900.2.4-03⁶). A standards based approach is intended to ensure that the regulations stay current, as standards are more easily amended than regulations.

The regulations require source establishments that handle, process, import and distribute human tissue to register with Health Canada and to confirm their compliance

¹ Safety of Human Cells, Tissues and Organs for Transplantation Regulations SOR-2007-118
<http://laws.justice.gc.ca/PDF/Regulation/S/SOR-2007-118.pdf>

² MDRs –Medical Devices Regulations (SOR/98-282) <http://laws.justice.gc.ca/PDF/Regulation/S/SOR-98-282.pdf>

³ Biologic & Genetic Therapies Directorate (BGTD) - Expert Advisory Committee - Cells, Tissues and Organs, Record of Meeting, Tuesday, March 20, 2007. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/brgtherap/mm_crr_2007-03-20-eng.pdf

⁴ CAN/CSA-Z900.1 Cells, Tissues, and Organs for Transplantation and Assisted Reproduction: General Requirement

⁵ CAN/CSA-Z900.2.2-03 Tissues for Transplantation

⁶ CAN/CSA Z900.2.4-03 Ocular Tissues for Transplantation

with the CTOs. Regulations mandate Canadian transplant establishments to source their allografts from establishments registered with Health Canada.

As part of the CTO regulatory framework, Health Canada will be introducing a compliance monitoring and enforcement program and a more comprehensive surveillance and adverse reaction reporting strategy. In 2005, Health Canada considered several options for compliance monitoring and enforcement including: licensing based on an application; licensing based on a Health Canada inspection; or licensing based on a third party inspection.⁷ Health Canada recently announced that inspections of CTO establishments will commence in 2009. Once all registered establishments have been inspected, a final Health Canada CTO inspection program will be established that is most appropriate for the CTO type and the variability that is associated with the activities performed by an establishment. A strategy for this program will be publicly available once it has been finalized but is not expected for several years.⁸

The Medical Device Regulations (MDRs) impose safety standards on the manufacture, importation, and distribution of more than minimally manipulated tissues, heart valves, and dura mater. These tissues are classified as Class IV Medical Devices, the highest risk category, and require a device license. MDR requirements include standards for safety & effectiveness, labeling, distribution records, complaint handling, mandatory problem reporting and recall, and implant registration. Manufacturers are also required to be in compliance with the ISO 13485:2003 quality system standard for medical devices and are inspected by third party registrars.

Each province and territory has a Human Tissue Gift Act or equivalent. These acts do not provide detailed quality or safety requirements for the tissue donation or transplantation process.

Quality within Canadian Tissue System

An effective quality management system ensures that products and services not only meet customer specifications but also conform to all regulatory and quality requirements. It extends beyond traditional quality control activities by establishing a more coordinated approach which controls product quality, guides continuous process improvement and provides the framework to comply with accreditation and regulatory requirements. There are many different quality system frameworks or models that can be used to meet these requirements including the ISO model⁹ or the AABB model.¹⁰ The most important issue is the thorough and consistent implementation of the elements within the chosen quality system framework.

⁷ Health Canada – Health Products and Food Branch, Proposed Options for Compliance Monitoring and Enforcement in Phase II, Presentation 9, 2005.

⁸ Health Canada – Cells, Tissue and Organs – Frequently Asked Questions, 2009

⁹ International Organization for Standardization. ISO9001:2000 Quality management systems - Requirements

¹⁰ AAAB DRAFT Updated Quality Management Standards

http://www.aabb.org/documents/Programs_and_Services/Standard_Setting_Activities/draftqmstandards.pdf 2009-09-15

Source Establishments

A 2009 environmental scan identified significant variation in the understanding and application of quality management systems in Canadian source establishments.¹¹ There are several contributing factors including the organizational setting of the tissue establishment, the type of allografts processed, and the establishment's participation in voluntary accreditation programs.

The regulatory requirements that apply to tissue banks as “manufacturers” of biological products are considerably different than the standards and requirements within the typical hospital environment. Tissue banks operating as one of many “services” within a large hospital can be challenged to obtain the specific resources required to meet the applicable regulatory and accreditation requirements. This risk is significant for smaller tissue programs such as in-hospital surgical bone banks that find it difficult to maintain quality assurance systems with limited hospital resources.¹² This is certainly one factor in the closure of many of the smaller surgical bone banks in recent years.^{5,13}

The type of allografts processed by the programs will also influence a program's approach to quality. For example, programs that process tissue regulated as medical devices are required to maintain a quality system compliant with the ISO 13485 quality standard. This standard requires controls in the work environment for product safety, inspection, and traceability for implantable devices, and verification of the effectiveness of corrective and preventive actions. Programs that are registered to this standard will have a highly structured approach to controlling product quality and monitoring and maintaining the effectiveness of their processes.

The American Association of Tissue Banks (AATB) and the Eye Bank Association of America (EBAA) accreditation programs have established rigorous standards to prevent disease transmission and ensure optimal clinical performance of transplanted cells and tissues. As of September 2009, 6/10 Canadian programs that process ocular tissue have EBAA accreditation and 7/21 banks that process musculoskeletal, cardiac or skin tissue in Canada have AATB accreditation.¹⁴ The latter is seen as an important indicator of a tissue program's ability to follow best known practices and to ensure safety.^{15,16}

The scan identified variations in transmissible disease testing, bacteriological testing, and bio-burden reduction and sterilization activities. Nucleic Acid Testing (NAT) is recommended within the CTOs, but not all programs are performing NAT even though there is evidence that this type of testing reduces the risk of undetected transmissible

¹¹ 2009 Environmental Scan of Canadian Tissue System, Canadian Blood Services.

¹² Canadian Council for Donation and Transplantation, Evaluation of Surgical Bone Banking in Canada, 2006

¹³ 2009 Environmental Scan of Canadian Tissue System, Canadian Blood Services.

¹⁴ Based on AATB and EBAA lists of accredited programs (September 2009) and Health Canada's List of Registered Cells, Tissues and Organs (CTO) Establishments – June 2009.

¹⁵ American Academy of Orthopaedic Surgeons (AAOS), Benefits of Musculoskeletal Allograft Tissue Outweigh Risks, 2003

¹⁶ Choosing a Tissue Bank: Considerations to Help Your Facility Choose an Allograft Tissue Provider, Northwest Tissue Centre – Puget Sound Blood Centre

diseases.¹⁷ There are differences in the sampling methods for bacteriological culture testing of tissue, and the sterility testing methodologies vary depending on the laboratory that each source establishment contracts to perform the work. Significant variation was identified in the bio-burden reduction and sterilization practices; this is not an issue as long as the process is appropriately validated. Recent literature on the topic of bacterial contamination and allograft processing and testing procedures emphasize the need for focused review in this area.^{17,18} Canadian tissue programs have been challenged by the in-depth research and validation work required to support effective bio-burden reduction practices.¹³

The majority of Canadian tissue banks process and distribute tissue only within their institution or region. Current processing steps and specific product characteristics are established based on input from regional end-users and local expertise and resources. There is very little formal interaction between tissue banks and broad based end-user groups. The sharing of best practices between programs and research and development activities to improve processing procedures and product characteristics is limited within the current system.¹⁹

Transplant Establishments

End-users of tissue and tissue products include orthopaedic surgeons, neurosurgeons, cardiovascular surgeons, ophthalmologists, oral & maxillofacial surgeons, periodontists and dentists. These end-users perform tissue transplants in various settings including hospitals, ambulatory care settings, office-based surgery programs and dental and periodontal offices. The wide range of tissue users and settings where tissues are transplanted translates into varied practices for selecting tissue vendors, acquiring tissue, tissue storage, maintenance of records for traceability purposes, and surveillance.

In the CTO regulations, transplant establishments are required to keep records of the tissues transplanted, including a description of the tissue and identification code, registration number of the source establishment, and information that captures the identification of the recipient. Records are to be maintained for any errors, accidents and adverse events, and the investigation and corrective actions taken in connection with those tissues. Unexpected adverse reactions must be communicated to source establishment and all CTO in its possession that could potentially cause an adverse reaction are to be quarantined. Tissue transplant establishments are not required to register with Health Canada and there is no process in place to audit their compliance with regulatory requirements.

¹⁷ Wolfenbarger L., Eisenlohr L. M. Ensuring the Safety of Allograft Tissue, LifeNet Health - Bio-Implants Division, June 2007

¹⁸ Eastlund T, Bacterial infection transmitted by human tissue allograft transplantation, Cell and Tissue Banking (2006) 7:147–166

¹⁹ 2009 CBS Environmental Scan

The current Accreditation Canada²⁰ standards for healthcare service organizations do not include detailed requirements related to tissue donation or transplantation. There is an effort underway to update and incorporate organ and tissue donation requirements within the existing standards and to create a stand alone set of standards focused specifically on Organ and Tissue Donation and Transplantation.

Based on the supply survey responses from the 2009 environmental scan work, only 3/20 hospitals (15%) that have tissue programs have a more centralized approach to managing and controlling tissue import, storage, issuing, and tracking. In some hospitals, the blood bank helps to manage tissue. Blood banks are familiar with managing regulated, biological products and understand the supporting quality elements required to store, issue, and track tissue products. The number of hospitals where this is occurring has not been assessed but it is expected that the percentage of blood banks fulfilling this role within Canadian hospitals would be lower than 15 percent.²¹

B. Current Community Thinking

I. Reports and Papers

Quality issues in tissue banking: Quality management systems – A review, 2000²²

This report describes the application of an ISO 9000 based quality management system in a tissue bank and the need for a broad quality framework that addresses research and development, design control, and management processes in addition to technical tissue banking standards. The concept of quality is linked with other goals such as the improvement of tissue characteristics, innovation and new product development, lowering of costs, satisfaction of surgeons, business competitiveness, and international cooperation.

The Joint Commission Accreditation Program: Hospital²³

The Joint Commission's tissue storage and issuance standards are applicable to hospitals, critical access hospitals, ambulatory care settings and office-based surgery programs, and address three major performance elements:

- organizations must assign responsibility for oversight of the tissue program throughout the establishment and define procedures to standardize systems and processes for acquiring, receiving, storing and issuing tissues;

²⁰ Accreditation Canada <http://www.accreditation.ca/accreditation-programs/gmentum/standards/> 2009-09-15

²¹ A web-based survey of US hospitals in 2005 identified that the blood bank was responsible for tissue in 164 of 904 hospitals (18%). Christopher Hillyer. Editorial; Tissue Oversight in Hospitals: the Role of Transfusion Services, *Transfusion* 2007;47:185-187.

²² von Versen R., Mönig H.-J., et al. Quality issues in tissue banking: Quality management systems – A review. *Cell and Tissue Banking* 1: 181–192, 2000

²³ The Joint Commission – Accreditation Program: Hospital http://www.jointcommission.org/NR/rdonlyres/FC01E2E0-A0CB-4A71-AF0B-137AA77D1BD6/0/AllChapters_HAP.pdf 2009-09-15

- organizations must maintain records for traceability to ensure sufficient retrieval of information in the event of an adverse patient reaction or manufacturer recall; and
- organizations must create a clearly defined process to investigate adverse events.

Clostridium infections associated with musculoskeletal-tissue allografts, 2004²⁴

This report notes that infections acquired through bacterial contamination of allografts have the potential to result in substantial complications or death. The study recommends that current regulations and standards for processing and testing allograft tissue need to be enhanced to prevent such life-threatening allograft-associated infections. Recommendations to tissue processors include processing tissue using a method that can kill bacterial spores. If no sporicidal method can be used (e.g., heart valves) processors should perform pre-processing cultures and discard tissue with enteric pathogens. The report also recommends that tissue banks should validate all methods used for tissue culture to ensure that carryover of residual antimicrobial agents does not result in false negative culture results.

Bacterial infection transmitted by human tissue allograft transplantation, 2006²⁵

This report notes that organizations setting the professional standards need to review their requirements for assuring sterility of allografts and for investigating and reporting allograft-associated infections. Countries need to decide whether voluntary professional standards are sufficient or whether governmental regulations are needed.

II. Forums

**National Consultation: Organ and Tissue Donation and Transplantation²⁶
(Canadian Blood Services)
September 22-24, 2008, Gatineau, Quebec**

This workshop focused on the central question, “Given the need for national, integrated services in tissue donation and transplantation (TDT), how do we establish a system that best meets the needs of Canadian patients?” The final output from this consultation listed a number of broad recommendations in relation to safety and quality including:

- ensure consistent interpretation of standards and regulations;
- develop a risk management system to identify potential safety risks;

²⁴ Kainer MA, Linden JV, Whaley DN, et al. Clostridium infections associated with musculoskeletal-tissue allografts. New England Journal of Medicine. 2004;350:2564-2571.

²⁵ Eastlund T, Bacterial infection transmitted by human tissue allograft transplantation, Cell and Tissue Banking (2006) 7:147-166

²⁶ Canadian Blood Services. Organ Donation and Transplantation Syntegration Consolidated Output. 2009.

- establish an integrated national quality program including a national measurement system and continuous quality improvement program; and
- provide quality support to supply chain process owners in order to obtain uniform quality and process improvement.

**Second Global Consultation on Regulatory Requirements for Human Cells and Tissues for Transplantation (HCCT): Towards Global Harmonization through Graduated Standards²⁷
(World Health Organization)**

June 2006, Geneva

Participants from 24 countries attended this meeting that focused on harmonizing global practices in the procurement, processing and transplantation of human cells and tissues. Some key points from this forum include:

- National or regional legislation or regulation for human cells and tissue is lacking in many geographical areas. The need for national oversight and for quality system approaches in the delivery of these services is critical.
- There is currently a major focus worldwide on the development of legal frameworks alongside organizational structures for oversight and regulation.
- There is a need for consultation and collaboration between health authorities and scientific and professional societies to optimize regulatory requirements and enforcement processes with the shared objective of guaranteeing real improvement in safety and quality while maximizing access to essential services.

C. Other Models

United Kingdom

The Human Tissue Authority (HTA) regulates organizations that process and store human tissue for patient treatment. The HTA has developed comprehensive standards that implement the requirements of the EU Tissues and Cells Directives. The standards require establishments that process tissue to obtain licenses from the HTA. In addition, any organization that stores tissues for longer than 48 hours is also required to have a license; a requirement unique to the UK regulatory framework. The HTA performs inspections of licensed tissue establishments at least once every two years.

NHSBT Tissue Services is the UK's major provider of human tissue for transplant and competes with other UK tissue banks and international providers for market share. As part of the blood service within the UK, the Tissue Services' quality program aligns closely with the program for blood. The blood and tissue 'business lines' share common

²⁷ Second Global Consultation on Regulatory Requirements for Human Cells and Tissues for Transplantation: Towards Global Harmonization through Graduated Standards²⁷ (World Health Organization) June 2006, Geneva

quality elements including document control, incident reporting, and the internal audit systems. The NHSBT Tissue Service has noted that their work in the area of quality assurance and their compliance efforts have been eased through being a part of an organization that is mature in these areas. In contrast, the independent cardiovascular tissue banks operating outside of the NHSBT Tissue Services have had to introduce technical and structural changes in order to meet the HTA regulatory requirements.²⁸ Within the UK, there are many other tissue programs outside of the NHSBT Tissue Services that process surgical bone, bone from deceased donors, and cardiac tissue that have their own quality programs to meet the regulatory requirements.

United States

The Food and Drug Administration regulates the tissue industry in the United States with the application of three different regulatory tools. The first is the requirement for establishment registration and listing. The second is the requirement to ensure donor eligibility by donor screening and testing and the third is the application of 'Good Tissue Practice' (GTP) to ensure that handling and processing controls prevent contamination and preserve tissue and cell integrity. The FDA has a well-developed inspection program to enforce regulatory requirements and provides information on these inspections back to the tissue community. Over half of all the tissue banks in the US were inspected by the FDA in 2007.²⁹ A Tissue Safety Team has also been established by the FDA with the primary purpose of providing a coordinated process for the review, investigation, and communication of report of HCT/P adverse reactions.

Tissue banking activity in the United States is more centralized than in Canada with concentrated resources, expertise, and specialization found in several large processors. While 82/109 tissue banks (75%) in the United States are AATB accredited, all 32 tissue banks (100%) that are performing tissue processing activities are AATB accredited.¹⁴ This indicates the presence of well-developed quality programs for all US processors. Seventy percent of banks that distributed ocular tissue are EEBA accredited.³⁰

Many hospitals in the United States follow The Joint Commission's hospital accreditation program. The Joint Commission evaluates participating hospitals against a set of standards that include detailed requirements on the management of tissue.

Quebec Model - Héma-Québec: The Cells, Tissues and Blood Model

The CTO regulations apply to Héma-Québec as a source establishment within Canada. Within Québec, the provincial Health Minister has extended Héma-Québec's mission to include tissues and has designated the organization as the human tissue supplier in the province.

²⁸ J. Davies, UK cardiovascular tissue processing—an overview. *Cell Tissue Banking* (2007) 8:307–327

²⁹ Robert Rigney. Report on the 2007 Annual Survey, American Association of Tissue Banks 13th Annual Spring Meeting, March 29, 2009.

³⁰ Based on data from the EEBA 2008 Statistical Report and the FDA's Human Cell and Tissue Establishment Registration List (Registered US establishments distributing corneas/sclera). <https://www.accessdata.fda.gov/scripts/cber/CFAppsPub/tiss/index.cfm>

The quality program that Héma-Québec has established aligns with their program for blood; these quality assurance processes and programs (e.g., supplier audits) have been successfully adapted to the tissue business line.

Canadian Blood Services Model (Blood Model)

The requirements applicable to Canadian blood suppliers are the *Good Manufacturing Practices Guidelines*³¹ and the *Annex to GMP Guidelines*³² specific to blood and blood components. Health Canada performs regular audits of all Canadian Blood Services centres to assess compliance to the regulations. All operational changes impacting the safety of the blood supply require review and approval by Health Canada prior to implementation.

The success of Canadian Blood Services has been in the institution of precautionary measures and the creation of a governance system that prioritizes safety.³³ Canadian Blood Services has a Quality and Regulatory affairs division responsible for developing the key processes of the quality management system including document control, change control, validation and deviation management. There is also a group dedicated to performing internal audits and audits of external suppliers. Each blood centre has a quality assurance unit responsible for maintaining the quality program and providing independent oversight to that site's operations.

³¹ Good Manufacturing Practices Guidelines 2002 http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/compli-conform/2002-gui-0001-eng.pdf

³² Good Manufacturing Practices for Schedule D Drugs, Part 1 Biological Drugs including fractionated blood products http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/sched_d_part1-annexe_d_part1_tc-tm-eng.php and Good Manufacturing Practices (GMP) for Schedule D Drugs, Part 2, Human Blood and Blood Components http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/sched_d_part1-annexe_d_part1_tc-tm-eng.php

³³ Kumanan Wilson MD MSc, The Krever Commission — 10 years later. CMAJ • November 20, 2007 • 177(11)

3. Analysis

A. Analysis Approach

The 2009 Environmental Scan of the Canadian tissue bank community including quantitative surveys, site visits, and qualitative interviews has been conducted to provide the basis for this document. Analysis of existing research and opinion papers has also been completed to inform discussions.

A quantitative survey (response rate 87%) of all Canadian tissue banks, excluding Québec, was undertaken to document 2008 activity. Site visits and telephone interviews have been conducted to obtain qualitative information on Canadian tissue activities.

Analysis of the solution design question will be undertaken to address two sub-questions:

1. How can the Canadian tissue system best ensure consistent safety and quality within source establishments?
2. How can the Canadian tissue system best ensure consistent safety and quality within transplant establishments?

The analysis was conducted with the understanding that regulatory framework for tissues is evolving in each of the countries assessed. It is also recognized that it is difficult to quantitatively compare the quality programs of each source establishment. Each establishment will address similar elements in their quality system; the differentiating characteristic is an establishment's ability to leverage their quality program to improve processes and products and prevent non-conformances. The presence or absence of the key quality elements and practices can be noted but the overall effectiveness of specific quality systems cannot be evaluated within this paper.

The analysis included an assessment of the strengths and weaknesses of the regulatory frameworks. Where information was available, the approach to quality management in source and transplant establishments was evaluated. A literature review identified specific areas of tissue banking practice not always present in the regulations that can influence the safety and quality of tissue and tissue use. Options were then identified and analyzed in terms of how they would address weaknesses raised in the assessment of the current state of source establishments and transplant establishments.

B. Findings

- The need for national oversight and for quality system approaches in the delivery of the tissue services is widely accepted.
- The key elements of all three regulatory frameworks examined have similar components but are in different stages of development and implementation. The compliance monitoring and enforcement program within the Canadian system is lagging behind the UK and the United States models.
- The comprehensiveness of the regulatory requirements in the three models evaluated differs in key areas. For example, the CTOs do not provide the same level of detailed requirements in the areas of quality management system implementation as the HTA Directives in the UK. The requirements for processing controls including validation and change control are more detailed in the GTP required by the FDA than in the CTO requirements.
- Certain programs in Canada have had more difficulty implementing the processes required in the new standards.
- Based on the regulatory requirements and the proportion of tissue banks that are AATB accredited, tissue banks in the United States generally have more advanced quality programs than Canadian tissue banks.
- The current regulations do not address all of the risks associated with bacterial contamination of allografts. Voluntary standards provide more detailed requirements for processing and testing procedures to address these risks, but not all programs adopt best practices.
- There is a need for regulatory or accreditation requirements to provide guidance to transplant establishments on the management of allograft tissue.

4. Options and Considerations

A. Options

I. How can the Canadian tissue system best ensure consistent safety and quality within source establishments?

a) Status Quo

Tissue banks are required to follow CTO regulations and can choose to obtain to be accredited to other voluntary standards (e.g., AATB, EBAA).

Strengths	Weaknesses
<ul style="list-style-type: none"> ▪ No resource requirements ▪ No change management 	<ul style="list-style-type: none"> ▪ No change in the quality and safety of activities managed by source establishments
Barriers	
<ul style="list-style-type: none"> ▪ No barriers to implementation as this option is the current state 	

b) Establish a nationally standardized quality program for all tissue banks.

Each element within a quality system framework could be standardized (e.g., document control, incident/non-conformance management, internal audit program, supplier qualification)

Strengths	Weaknesses
<ul style="list-style-type: none"> ▪ Provides a framework to share quality and risk management expertise ▪ Provides a framework for the management of emerging issues and ensures all programs are responding to the issue. ▪ The overall resource requirements may be lower when compared to the cost of each individual program establishing its own independent, yet robust quality management system 	<ul style="list-style-type: none"> ▪ Centralized decision making can act as a barrier to efficiency ▪ Implementation of a standardized quality system can inhibit programs from addressing local challenges and incorporating local ideas and knowledge

Barriers
<ul style="list-style-type: none"> Most tissue banks in Canada are in a hospital setting and are linked in some way to existing hospital services or departments. It would be difficult to establish an overarching quality program with the existing linkages

c) Centralized national support of distinct quality programs at each tissue bank.

An independent quality system is maintained by each tissue bank. A mechanism for centralized national support of distinct quality programs at each tissue bank would need to be established. Standards and programs could be instituted for specific quality components (e.g., validation, auditing, measurement, and metrics).

Strengths	Weaknesses
<ul style="list-style-type: none"> Assistance provided to tissue banks to improve specific areas where they may not have expertise (e.g., auditing, validation) Provides a framework for measurement and benchmarking activities Standardization of specific quality elements within quality programs 	<ul style="list-style-type: none"> Overall resource requirements to implement and maintain independent quality programs at each site may be higher than a standardized approach
Barriers	
<ul style="list-style-type: none"> Most tissue banks in Canada are in a hospital setting and are linked in some way to existing hospital services or departments. It would be difficult to establish coordinated support of distinct quality programs Obtaining consensus on the components of the quality program requiring support 	

II. How can the Canadian tissue system best ensure consistent safety and quality within transplant establishments?

a) Status Quo

Minimal regulatory oversight for transplant establishments that do not recover organs or distribute CTOs. No detailed Canadian accreditation standards related to transplant establishment activities.

Strengths	Weaknesses
<ul style="list-style-type: none"> No resource requirements No change management 	<ul style="list-style-type: none"> No change in the quality and safety of processing activities and of the use of allografts
Barriers	
<ul style="list-style-type: none"> No barriers to implementation as this option is the current state 	

b) Update Accreditation Canada (AC) standards

Include detailed tissue requirements in the relevant standards that align with the Joint Commission’s requirements on tissue. These requirements for hospitals would include the implementation of oversight of the tissue program including procedures for acquiring, receiving, storing, and issuing tissues. The standards would also include requirements for traceability and defined processes for adverse patient reactions and recalls.

Strengths	Weaknesses
<ul style="list-style-type: none"> ▪ Forces participating hospitals that use allograft tissue to establish an oversight structure and processes for managing tissues 	<ul style="list-style-type: none"> ▪ A significant change for the majority of Canadian hospitals to establish systems and processes to manage tissue ▪ AC standards are voluntary; hospitals that do not participate in Accreditation Canada programs are not required to adhere to the standards ▪ Focuses primarily on the hospital use of allografts and does not address allografts used in other in settings (e.g., dental clinics)
Barriers	
<ul style="list-style-type: none"> ▪ Acceptance of the detailed tissue requirements for tissue within the healthcare community 	

B. Considerations

- During the 2009 Environmental Scan conducted by Canadian Blood Services, a number of tissue programs noted that they would like to further develop their quality programs or would value assistance in the application of quality management systems.
- Quality programs are generally aligned with the business model of the organizations. Examples of national or regional quality programs where the governance structure is not also aligned for the country or region have not been identified.

Appendix A

Regulatory Framework & Oversight Summary

	United States	United Kingdom	Canada
Strengths	<ul style="list-style-type: none"> Comprehensive requirements with the application GTP Well developed inspection program Feedback provided to tissue community on inspections, recalls and adverse events Guidance documents provided to assist the tissue community in dealing with emerging issues Flexibility built into requirements to reflect the changing environment 	<ul style="list-style-type: none"> Well developed inspection program Some oversight of transplant establishments Detailed Quality Management System requirements Regulatory framework aligns with EU standards 	<ul style="list-style-type: none"> Standards based to allow changes to be incorporated without changing the regulations Safety standards address donor screening; donor testing; donor suitability assessment; retrieval; processing and storage; packaging and labeling; and error, accident and adverse reaction reporting.
Weaknesses	<ul style="list-style-type: none"> No regulatory oversight of transplant establishments 	<ul style="list-style-type: none"> Some regulatory oversight of transplant establishments (if establishments store tissue for > 48 hours) National information on inspections, recalls or adverse events not disseminated to the tissue community 	<ul style="list-style-type: none"> Only specific sections of the CSA Standards are required to be implemented The ability to keep requirements current is dependant on the CSA standards process No GTP focus in current regulations. Regulations lack detail on many areas including supply/supplier qualification, in-process controls and change/process management Minimal oversight of establishments using tissue Inspection program not well developed National information on inspections, recalls or adverse events not disseminated to the tissue community

Appendix B

A Comparison of Selected Elements in Regulations

Note: The standards have been summarized for the purpose of comparison; the full wording of each requirement is not present within the table.

Registration

Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P's) – United States	Safety of Human Cells, Tissues and Organs for Transplantation Regulations - Canada	HTA Direction 002/2007 - United Kingdom
<p>1271.10 b) If you are a domestic or foreign establishment that manufactures an HCT/P described in paragraph (1271 a): (1) You must register with FDA; (2) You must submit to FDA a list of each HCT/P manufactured; and (3) You must comply with the other requirements contained in this part.</p> <p>1271.15 Key exceptions (d) You are not required to comply with the requirements of this part if you are an establishment that does not recover, screen, test, process, label, package, or distribute, but only receives or stores HCT/P's solely for implantation, transplantation, infusion, or transfer within your facility. (f) You are not required to register or list your HCT/P's independently, but you must comply with all other applicable requirements in this part, if you are an individual under contract, agreement, or other arrangement with a registered establishment and engaged solely in recovering cells or tissues and sending the recovered cells or tissues to the registered establishment.</p>	<p>5. (1) Every establishment must be registered under these Regulations, except a retrieval establishment and a transplant establishment. Note: A transplant establishment that distributes cells, tissues or organs must be registered.</p> <p>6. (1) An application for registration of an establishment must be made and must include details on the establishment and certification that the establishment is in compliance with the CTO regulations.</p>	<p>14. The HTA is regulating establishments that store, procure, test, process, distribute, import or export tissues and / or cells intended for human application via the Regulations by:</p> <p>a. Requiring persons who store tissues and / or cells intended for human application to obtain and maintain a licence from the HTA;</p> <p>b. Requiring persons carrying out the activities of procurement, testing, processing, distribution, import or export of tissues and / or cells intended for human application to carry out such activity or activities under the authority of a licence granted by the HTA under the Regulations or alternatively in pursuance of a third party agreement; and</p> <p>c. Where the activities of procurement, testing, processing, distribution, import or export of tissues and / or cells intended for human application are carried out in pursuance of a third party agreement, requiring the LH and the DI to ensure that third party agreements are maintained in accordance with the requirements of the Regulations and these Directions and that appropriate SOPs are in place and complied with in accordance with the requirements of the Regulations and Directions.</p>

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Control of Establishments performing work for a Source Establishment

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<p>1271.150 - Current good tissue practice requirements.</p> <ul style="list-style-type: none"> -requirement for establishment under a contract, agreement, or other arrangement that performs any step in manufacture to comply with Current Good Tissue Practice requirements (CGTP) requirements. -Requirement to assess an establishment for compliance with CGTP before entering into a contract, agreement for the establishment to perform any step in manufacture and to monitor in an on-going basis compliance with requirements. -If you ensure HCT/P meets all release criteria and make HCT/P available for distribution, you are responsible for reviewing manufacturing and tracking records to determine compliance with the GTP requirements and all other applicable requirements. 	<p>15. A source establishment is responsible for the processing of CTOs, whether the processing is carried out by the source establishment itself or by another establishment, and for determining whether the CTOs are safe for transplantation.</p>	<p>68. The establishment shall put in place and maintain written agreements with third parties whenever an activity takes place which has the potential to influence the quality and safety of human tissues and cells processed.</p> <p>69. The establishment shall evaluate and select third parties on the basis of their ability to meet the requirements of these directions and the parent directive.</p> <p>70. The establishment shall keep a complete list of agreements established with third parties.</p>

Note: Detailed requirements for source establishments to evaluate and maintain written agreements with outside establishments that perform work for them are not present in the CTO regulations.

Quality Management System Requirements

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<p>1271.160 - Establishment and maintenance of a quality program.</p> <p>If you are an establishment that performs any step in the manufacture of HCT/Ps, you must establish and maintain a quality program. The quality program must address all core CGTP requirements. Requirements include:</p> <ul style="list-style-type: none"> -Establishing and maintaining appropriate procedures relating to core CGTP requirements -Ensuring that procedures exist for receiving, investigating, evaluating, and documenting information relating to core CGTP requirements, including complaints, and for sharing any information pertaining to the possible contamination of the HCT/P or the potential for transmission of a communicable disease by the HCT/P with the appropriate establishments (e.g. recovery organizations) -Ensuring that appropriate corrective actions relating to core CGTP requirements, including reaudits of 	<p>70. Quality assurance requirements (Sections 71 to 76) apply only to establishments that distribute cells, tissues or organs.</p> <p>71. Ensure that a quality assurance system in place that complies with the requirements of these Regulations for all activities carried out.</p> <p>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.</p> <p>Requirements</p> <p>73. The standard operating procedures must be in a standardized format, reviewed and approved, available to personnel. Change to procedure must be approved by the medical director or scientific director before being implemented; and be kept up-to-date.</p> <p>74. An establishment must review its standard operating procedures every two years and again after any amendment to these Regulations or if a deficiency in a</p>	<p>18 The establishment shall put in place and maintain a documented quality management system which is applied to the activity or activities for which it is licensed in accordance with the standards laid down in the EU Directives and HTA Directions.</p> <p>19. The establishment's management shall be committed to the establishment, maintenance and continual improvement of the quality management system and shall in particular:</p> <ol style="list-style-type: none"> a. Set, maintain and update quality objectives; b. Appoint a quality manager who is suitably qualified and responsible for ensuring that the quality management system maintained by the establishment is implemented throughout the establishment and continually updated and improved in accordance with the principles of good practice and HTA Directions. The person

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<p>deficiencies, are taken and documented, as necessary. Verify corrective actions to ensure that such actions are effective and are in compliance with CGTP.</p> <ul style="list-style-type: none"> -Establishing and maintaining appropriate monitoring systems as necessary to comply with the requirements of this subpart (e.g., environmental monitoring); -Investigating and documenting HCT/P deviations (incidents) and trends of HCT/P deviations relating to core CGTP requirements and making reports if required under 1271.350(b) or other applicable regulations. -Periodically perform for management review a quality audit of activities related to core CGTP requirements. -Validate the performance of computer software (custom or customized software) for the intended use, and the performance of any changes to that software for the intended use if you rely upon the software to comply with core CGTP requirements 	<p>standard operating procedure is identified.</p> <p>75. An establishment must keep records that demonstrate that it has implemented its standard operating procedures.</p> <p>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.</p>	<p>appointed as quality manager in accordance with this sub paragraph may be an existing member of staff with other duties provided he / she can fulfil the duties of quality manager and is suitably qualified;</p> <ul style="list-style-type: none"> c. Establish a quality policy which incorporates the requirements of the Directives, Directions 001/2006 and these Directions, as amended from time to time, the principles of good practice and the health, safety and welfare of personnel of, and visitors to, the establishment and intermediate and end users of the tissues and / or cells; d. Conduct regular management reviews of the establishment's quality management system and document the results of the review including all decisions and actions agreed and taken to improve the effectiveness of the quality management system and service provided by the establishment; e. Make available the necessary resources in terms of facilities, personnel, equipment and materials and data and information systems to ensure the effective implementation and continual improvement of the establishment's quality management system; and f. Ensure that the organisational chart including the responsibilities and reporting relationships are communicated to all personnel within the establishment and that all personnel are aware of the importance of ensuring that the quality management system maintained by the establishment is effective and continually improved as appropriate
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Note: The HTA requirements for organizational and management support of a quality management system mirror the ISO9001:2000 quality management system requirements. These requirements support the introduction of quality culture in an organization and ensure that resources are dedicated to maintaining and improving the quality program. In contrast, the quality management system requirements in the CTO regulations list the procedural and record keeping standards but do not address organizational support of quality management systems.

Facilities and Environmental Monitoring

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<p>1271.190 - Facilities.</p> <ul style="list-style-type: none"> -Facility for manufacture must be of suitable size, construction, and location to prevent contamination of HCT/Ps 	<p>65. Facilities</p> <p>Facilities must be constructed and maintained to permit all of the following:</p> <p>(a) the carrying out of all of its activities;</p>	<p>35 The establishment shall have facilities and premises suitable for the carrying out of the activity or activities for which it is licensed, including, as appropriate, clinical</p>

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<p>-Maintain facility in a clean, sanitary, and orderly manner</p> <p>-Divide facility into separate or defined areas of adequate size for each operation, or you must establish and maintain other control systems to prevent improper labeling, mix-ups, contamination, cross-contamination, and accidental exposure of HCT/Ps to communicable disease agents.</p> <p>-Maintain procedures and records for above activities.</p> <p>1271.195 - Environmental control and monitoring.</p> <p>-Where appropriate, you must provide for the following control activities or systems:</p> <ol style="list-style-type: none"> (1) Temperature and humidity controls; (2) Ventilation and air filtration; (3) Cleaning and disinfecting of rooms and equipment to ensure aseptic processing operations; and (4) Maintenance of equipment used to control conditions necessary for aseptic processing operations . <p>-Inspect each environmental control system periodically to verify that the system, including necessary equipment, is adequate and functioning properly.</p> <p>-Monitor environmental conditions where conditions could reasonably be expected to cause contamination or cross-contamination of HCT/Ps or equipment, or accidental exposure of HCT/Ps to communicable disease agents. Where appropriate, you must provide environmental monitoring for microorganisms</p> <p>-Maintain records for above activities.</p>	<ol style="list-style-type: none"> (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. 	<p>facilities, laboratory facilities, storage facilities, facilities for reception and procurement, facilities for distribution, import and / or export, where relevant facilities for donation, and facilities for staff.</p> <ol style="list-style-type: none"> 36. The establishment shall put in place and maintain an SOP for the maintenance of its premises and facilities, which includes controlled access to premises and facilities, as appropriate; Cleaning and maintenance of all facilities; Regular audit of facilities; Disposal of waste, including clinical waste; 37. Specific requirements for clinical facilities including facilities that are suitable and appropriate for the activity or activities for which the establishment is licensed and that processing takes place in an environment with specified air quality and cleanliness in accordance with paragraphs 39 to 42 below (as applicable to license) 38. Specific requirements for laboratory facilities including providing a safe working environment for all staff in accordance with national legislation and guidelines; and where processing is to take place in an environment with a specified air quality and cleanliness (as applicable to license); 39. The establishment shall ensure that processing (if applicable to license) takes place in an environment with specified air quality and cleanliness to minimise the risk of contamination, including cross contamination between donations, and to protect their quality and safety at all times. The establishment shall validate and monitor the effectiveness of these measures at appropriate intervals. 40. Unless otherwise specified in paragraph 41 below, where tissues or cells are exposed to the environment during processing, without a subsequent microbial inactivation process, an air quality with particle counts and microbial colony counts equivalent to those of Grade A as defined in the current European Guide to Good Manufacturing Practice (GMP), Annex 1 and EU Directive 2003/94/EC is required with a background environment appropriate for the processing of the tissue or cell concerned, but at least equivalent to GMP Grade D in terms of particles and microbial counts. 41. A less stringent environment than specified in paragraph 40 above may be acceptable where: – <ol style="list-style-type: none"> a. A validated microbial inactivation or validated terminal sterilisation process is applied; b. Or, where it is demonstrated that exposure in a Grade A environment has a detrimental effect on the required properties of the tissue or cell concerned; c. Or, where it is demonstrated that the mode and route of application of the tissue or cell to the recipient
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implies a significantly lower risk of transmitting bacterial or fungal infection to the recipient than with tissue and / or cell transplantation; and
d. Or, where it is not technically possible to carry out the required process in a Grade A environment

Note: The CTO Regulations require establishments to perform environmental monitoring as appropriate to their work, but do not provide detailed environmental control or monitoring requirements.

Process Control and Validation

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<p>1271.225 - Process changes.</p> <ul style="list-style-type: none"> ▪ Any change to a process must be verified or validated to ensure that the change does not create an adverse impact elsewhere in the operation, and must be approved before implementation by a responsible person with appropriate knowledge and background. <p>1271.230 - Process validation.</p> <ul style="list-style-type: none"> ▪ Where the results of processing cannot be fully verified by subsequent inspection and tests, validate and approve the process. ▪ Any written representation that your processing methods reduce the risk of transmission of communicable disease by an HCT/P (e.g. sterility or pathogen inactivation of an HCT/P), must be based on a fully verified or validated process. ▪ When changes to a validated process occur, you must review and evaluate the process and perform revalidation where appropriate. 	<p>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.</p> <p>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.</p>	<p>50.</p> <p>a. The critical processing procedures must be validated and must not render the tissues and / or cells clinically ineffective or harmful to the recipient. This validation may be based on studies performed by the establishment, or on data from published studies or, for well established processing procedures, by retrospective evaluation of the clinical results for tissues and / or cells supplied by the establishment;</p> <p>b. It has to be demonstrated that the validated process can be carried out consistently and effectively in the establishment's environment by the establishment's personnel;</p> <p>c. The procedures must be documented in SOPs which must conform to the validated method and to the appropriate standards</p> <p>d. It must be ensured that all processes are conducted in accordance with the establishment's approved SOPs;</p> <p>e. Where a microbial inactivation procedure is applied to the tissues and / or cells, it must be specified, documented, and validated;</p> <p>f. Before implementing any significant change in processing, the modified process must be validated and documented;</p> <p>g. The processing procedures must undergo regular critical evaluation to ensure that they continue to achieve the intended results</p>

Note: Outside of the requirements relating to document control and the general requirement listed above (16), the CTO Regulations do not provide detailed change control requirements or process validation requirements.