



**WORLD HEALTH ORGANIZATION**

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First Global Consultation on  
Regulatory Requirements for  
Human Cells and Tissues for Transplantation

Ottawa, 29 November to 1 December 2004

**Report**

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# **Report**

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Regulatory Requirements for  
Human Cells and Tissues for Transplantation

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## **Introductory Note from the Secretariat**

This publication reports on the deliberations and outcomes of the first Global Consultation on Regulatory Requirements for Human Cells and Tissues for Transplantation, held in Ottawa from 29 November to 1 December 2004. The Ottawa meeting represents the first step in WHO involvement in harmonizing global practices in the procurement, processing and transplantation of human cells and tissues, along the requirements of World Health Assembly Resolution WHA57.18 on Human Organ and Tissue Transplantation adopted in May 2004.

This meeting was made possible thanks to the support of the Canadian Ministry of Health, through Health Canada and the Public Health Agency of Canada. We gratefully acknowledge this aid and, in particular, we wish to thank the staff of these two organizations for their efficient assistance in preparing and supporting the consultation.

This report represents the views of the participants, not necessarily those of WHO. The report was prepared by the undersigned with the efficient administrative and secretarial support of Christine Faivre-Pierret. It is based on a draft prepared by the meeting Rapporteurs, Deirdre Fehily and Jill Hartzler-Warner, with the assistance of Martha Wells, who deserve thanks for their dedication and their success at capturing and summarizing complex material with clarity. Deirdre Fehily also played an important role in the preparation of this consultation and her input is gratefully acknowledged. All the participants in the consultation should be thanked for their active participation and their will to achieve consensus. The Secretariat owes special thanks to the Chairman of the meeting, Elwyn Griffiths, for his steady and thoughtful chairmanship.

The report was submitted to all participants for comment. We are grateful to them for their input. Any error or omissions are, of course, our responsibility, not theirs.

Luc Noël, Coordinator, HTP/EHT/CPR



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## Executive Summary

Cells and tissues for transplantation (CTTx) constitute a specific class of health products with important therapeutic value, as they have in many cases no equivalent in restoring life-supporting or essential functions. Yet many countries have poor access to essential CTTx, such as cornea. At national level in most countries CTTx activity data is not available. Many countries are lacking regulatory frameworks for CTTx despite the inherent disease transmission risks associated with the transplantation of human material. Many CTTx are circulating across international boundaries to meet patient needs, in physical or immunological characteristics, or simply to bridge a supply gap. A large proportion of these CTTx circulate outside of any regulatory oversight.

World Health Assembly Resolution WHA 57.18 urges Member States to "implement effective national oversight of procurement, processing and transplantation of human cells, tissues and organs, including ensuring accountability for human material for transplantation and its traceability". The development of regulations and planning for CTTx services are the responsibility of health authorities in order to ensure protection of the donor, patient safety and clinical efficacy. Beyond outcomes for the donor and the recipient, current developments in the area of cellular therapy and tissue engineering need to progress in a clear regulatory environment. The benefits of implementing a comprehensive regulatory framework outweigh the cost of the necessary investment.

A comprehensive regulatory framework encompasses defining a system of reference, such as standards, providing specifications for CTTx which should be legally mandated, a system for ensuring compliance and enforcement, surveillance system and accreditation. It is important that regulation address public and private activities alike. Both should be associated with the process of reaching an agreement on requirements and best practices, in particular through the input of professional societies and all stakeholders.

Requirements for CTTx must balance high quality with the need to ensure availability and must not limit innovation or serve as a barrier to international exchanges.

Participants in the consultation examined first drafts of core global specifications for basic essential tissue and cell products that are used globally and are moved between countries or marketed commercially (frozen bone or tendon, freeze-dried bone, skin, amniotic membrane, cryopreserved cardiac valves and vascular segments, cornea, fresh haematopoietic stem cells, cryopreserved allogeneic unrelated cord blood stem cells and cryopreserved autologous or directed cord blood stem cells). These drafts were based on existing standards and regulations, they address donor selection, testing, contamination control, packaging and labelling. They will aim at describing core requirements within reach of any country, irrespective of resources, and should allow the achievement of a first step towards harmonization and define acceptable limits. The drafts, incorporating suggestions from the meeting, will be submitted to further expert consultation and will be proposed for consideration by the WHO Expert Committee on Biological Standardization.

At the level of cell and tissue establishments and clinical users, a quality management system is necessary to control the process from donor selection to clinical outcomes. This constitutes the essential requirements for cell and tissue establishments. There are several well-developed and tested quality systems applicable to cell and tissue banking. They must be

thoroughly and consistently implemented in all their elements, particularly with regard to traceability, adequate documentation and adverse events reporting and investigation.

Adverse events reporting should be incorporated at an early stage into the implementation of the regulation of CTTx. The human origin, the risk of transmissible agents, the susceptibility to microbial contamination and in general the limited experience in clinical trials of processing methods or clinical use have made vigilance and surveillance a major component of ensuring the safety of CTTx. Surveillance is essential in the development of transplantation strategies and policies. It should be active and comprehensive, not only limited to adverse events reporting, and would provide an opportunity for valuable collaboration of clinicians, operators, regulators and health authorities. Considering the international circulation of CTTx, and also the international circulation of individuals and the global nature of infectious threats, effective surveillance requires international collaboration. As part of WHO's strategy, and consistent with the requirements of Resolution WHA57.18, a Global Knowledge Base on Transplantation will be developed with Member States, which will address practices, safety, quality, efficacy, epidemiology and ethical issues.

The considerable experience of managing and regulating CTTx banking activities in some developed countries provides invaluable guidance to other countries as they embark upon this task. The meeting provided the key elements of an Aide Mémoire for CTTx services and their oversight by national regulatory authorities. Comprehensive oversight of cell and tissue transplantation activities will ensure inspection and the authorization of CTTx establishments. In developed countries many CTTx establishments were obliged to close as they could not comply with quality and safety requirements, due to their limited resources. It is essential that countries now developing their CTTx services plan for centralized cell and tissue banks, which are capable of effectively implementing quality systems while ensuring patient access.

The Ottawa consultation marks the first step in international harmonization of CTTx. As cell and tissue transplantation services develop and increase in scale globally, WHO will develop its activities to assist Member States in achieving the optimal level of quality, safety and efficacy of human tissue and cell products in a harmonized manner at global level.

## Opening Session

The Honourable Robert G. Thibault, Parliamentary Secretary to the Minister of Health, of Canada, welcomed delegates to Canada and the first Global Consultation on Regulatory Requirements for Human Cells and Tissues for Transplantation. He noted the challenges facing the global community, including new health and disease trends, the importance of innovation and the reality of doing more with less. Mr Thibault also stressed the opportunity of international cooperation to distribute to many the health and economic benefits that come from a solid regulatory environment. He noted that such cooperation could also heighten our collective ability to manage risks. Mr Thibault stated that it is an honour for Health Canada to host the consultation with the Public Health Agency of Canada (PHAC) and the World Health Organization (WHO).

On behalf of Dr David Butler-Jones, Canada's Chief Public Health Officer, Dr Paul Gully, Senior Director General of the PHAC, welcomed delegates. Dr Gully stressed the importance of a comprehensive surveillance system that can monitor outcomes and risks associated with transplants. He identified the partnership between the PHAC and Health Canada to develop a surveillance system that will help track and manage adverse events associated with cell and tissue transplantation as a promising model. He noted Canada's commitment to working with WHO to enhance the safety of cells and tissues and to protect public health.

Dr Luc Noël next addressed the delegates, presenting the remarks of Dr Vladimir Lepakhin, WHO's Assistant Director General in charge of the Cluster of Health Technology and Pharmaceuticals, who was unable to attend. Dr Lepakhin thanked the Government of Canada, Health Canada and the Public Health Agency of Canada for their generous support in helping to make it possible to bring together 48 experts, policymakers and regulators from 26 countries throughout the world to what will be viewed as an important milestone in the development of global regulatory requirements for human cells and tissues. Dr Lepakhin highlighted the three important considerations that led to WHO's involvement in the area of human cell, tissue and organ transplantation and the World Health Assembly Resolution (WHA57.18) adopted in May 2004. Dr Lepakhin noted that of these three concerns – ethics, access and the need for safety, quality and efficacy in this field – the last is the focus of the immediate consultation. He expressed his hope that this first meeting will produce globally-agreed baseline requirements for the safety and quality of cells and tissues and provide Member States with the tools to optimize cell and tissue transplantation services.

The delegates elected Dr Elwyn Griffiths from Health Canada Chairperson of the meeting and Dr Deirdre Fehily, from the National Transplant Centre in Italy, and Ms Jill Hartzler-Warner, from the United States Food and Drug Administration, as Rapporteurs.

## **Session 1: Introduction**

### **Background to WHO involvement in transplantation**

Dr Luc Noël provided an overview of the history, mission, core functions and organizational structure of WHO. He described the composition and responsibilities of the World Health Assembly (WHA) and the Executive Board (EB) and its initiatives to date in the field of transplantation.

In 1991 WHO published Guiding Principles on Organ Transplantation endorsed by the WHA (Resolution WHA44.25). These Guiding Principles were based on three major precepts:

- that organs should come preferably from deceased persons (though living adult donors may be used with consent)
- that living donors should generally be genetically related to recipients, and
- that no payment may be given or received for organs (though the cost of recovery, preservation and supply may be paid).

At the WHO Executive Board Meeting in January 2003, the Spanish member stressed the need for WHO to dedicate some of its budget to improving the quality of transplanted material and the Colombian member requested that the Director-General address ethical and technical issues in tissue banking. Subsequently, a background paper on Human Organ and Tissue Transplantation (EB112) was submitted to the Board.

Following wide consultation on the subject, WHO organized a meeting of experts which was held in Madrid in October 2003, with the support of the USA and Spain. At this meeting 37 clinicians, ethicists, social scientists and government officials from 23 countries, representing all WHO Regions and all levels of economic development, closely analysed issues of global concern in relation to the ethics, access and safety of tissue and organ transplantation.

The Report of the Madrid Conference highlighted some of the key challenges to be faced in tissue banking and transplantation globally. They included:

- the existence of tissue trafficking on a global basis
- poor levels of education, training and research in tissue banking globally
- limited or non-existent evidence for efficacy of transplantation of some tissues
- unregulated commercialization
- inability to always provide 'origin to destiny' traceability of tissues
- lack of harmonization of regulatory standards resulting in high costs for tissue banks, and
- concern regarding self-sustainability of 'not-for-profit' banks on the one hand while preventing excessive income of 'for-profit banks' using altruistically-donated human material.

The Madrid Report proposed that WHO could play an essential role in the global effort to address these issues. The following were identified as the key areas in which WHO could lead:

- Promotion of discussion between regulators to create an agreed definition of cells and tissues and to provide model regulatory framework options for Member States.
- Provision of guiding principles for the transparent regulation of ethical, organizational and technical aspects of tissue and cell transplantation, in order to increase both access and safety for patients.
- Promotion of the development of sustainable models of regulation, capacity building, training and surveillance and facilitating regional and global cooperation.
- Facilitation of global networking, cooperation and international data exchange on the therapeutic use of human tissues.
- Advocacy, support in identifying relevant needs and support for capacity building, specifically for cornea transplantation.
- Harmonization of the international regulation of haematopoietic stem cells, critical to continued global interchange of HLA-matched donations.

The report of this meeting was accepted by the WHO Executive Board and on 22 May 2004 and the World Health Assembly adopted a Resolution recommending WHO action. The Resolution, WHA57.18, is shown at Appendix 1.

The 11<sup>th</sup> International Conference of Drug Regulatory Authorities (ICDRA) held in Madrid, 16-19 February 2004, also produced a report highlighting the global need for greater regulation in the field of human tissue transplantation. It noted that the transplantation of human cells, tissues and organs has become the treatment of choice for a wide range of both fatal and non-fatal diseases and that the volume and complexity of activities relating to transplantation are growing rapidly. It stressed that the ethical and safety risks inherent in transplantation require effective regulatory oversight at national level and international cooperation. It called on Member States to develop and implement effective national regulation of procurement, processing and transplantation of human cells, tissues and organs, together with effective surveillance systems.

The ICDRA report also requested that WHO take an active role in facilitating global initiatives in the regulation of cell and tissue transplantation by:

- developing clear guidelines for the quality, safety and efficacy of human cell, tissue and organ transplantation, and
- facilitating national surveillance activities through the development of appropriate written standards and reference materials.

Dr Noël provided the meeting with an overview of the way WHO operates. Global reference material is developed through international consultation with health authority representatives, individual experts, operators and regulators in all parts of the world. WHO provides safety information globally through surveillance and alerts and the maintenance of global databases. At the request of Member States, WHO may provide support in the formulation of regional/national consensus and standards and in capacity building. It works to achieve global objectives through collaboration with health authorities in Member States, international governmental and non-governmental organizations and through WHO Collaborating Centres within Member States.

WHO objectives in the field of allogeneic transplantation were summarized as follows:

- To update and complete the 1991 WHO Guiding Principles on the basis of evidence (reviewing particularly the guidance on live donations and living donor outcome in various settings).
- To promote effective oversight of transplantation by national health authorities, taking account of the importance of self-sufficiency and the prevention of exploitation of the vulnerable.
- To facilitate harmonization of practices in transplantation including the safety, quality and efficacy of human material for transplantation.
- To encourage donation of human material for transplantation and access to essential transplantation.
- To foster the emergence of a global consensus on transplantation by bringing together experts and health authorities in each WHO Region to form a Global Forum on Transplantation.

This Global Transplantation Forum (GTF) would bring together all stakeholders: international governmental organizations, policy makers, national regulatory authorities, scientific bodies, relevant NGOs, the pharmaceutical industry involved in transplantation support and, if appropriately identified, recipients' and donors' representatives. It would facilitate information exchange, analyse the current situation in transplantation worldwide and identify issues and potential solutions. WHO would ensure broad dissemination of the GTF's findings.

## **Objectives, Scope and Expected Outcomes for the Consultation**

Dr Noël summarized the major objectives of the consultation as follows:

- To agree on an initial list of human cell and tissue products for transplantation (CTTx).
- To agree on basic global requirements for the organization of CTTx procurement, banking, issuing and transplantation and their regulatory oversight, including vigilance.
- To examine existing requirements for CTTx and identify core safety, quality and efficacy elements that could form global specifications for basic minimally-processed products, for submission to the WHO Expert Committee on Biological Standardization (ECBS).
- To identify further WHO initiatives that would improve access to safe and effective CTTx globally.

The participants in this consultation comprised an international group of stakeholders in cell and tissue transplantation from developed and developing countries. The group included policy makers, representatives of national regulatory and public health authorities, representatives of national transplantation agencies, operators, tissue banking experts and specialists in clinical transplantation.

The objectives had the overall aim of meeting patients' needs in the four major areas of concern: Quality, Safety, Efficacy and Access, thus justifying public trust in donation and in the institutions involved.

It was noted that the scope of this consultation did not include ethical issues, such as those relating to procurement, consent or payment, except in so far as they impact on safety, quality, efficacy and access. Such issues would be addressed at a projected global consultation on ethical issues in cell and tissue transplantation. Also excluded from the scope would be organs, tissue-engineered medicinal products, embryonic and foetal materials and gametes.

The consultation would focus, rather, on cells and tissues for transplantation that involve individual production (as opposed to mass production), are often patient-specific and where global circulation may be a necessity. The transplantation of these tissues and cells carries an infectious risk. The prevention of pathogen transmission, traceability from donors to recipients and surveillance of recipient adverse events are therefore essential requirements. Shortages of CTTx for vital needs are also a key concern for the consultation.

WHO Resolution WHA57.18 calls for 'National oversight of procurement, processing and transplantation of human cells, tissues and organs, including ensuring accountability for human material for transplantation and its traceability'. The Ottawa consultation should be a starting point on the road to achieving this objective globally. The steps would be:

- To identify essential requirements attainable in any context.
- To capture consensus, in particular in existing reference documents at national and regional level and from scientific/professional societies.
- To identify aims and priorities for cell and tissue transplantation services.
- To initiate a global network bringing together stakeholders worldwide for the benefit of patients.

### **Cell and Tissue Regulatory Oversight – the Example of Canada**

Ms Liz Anne Gillham-Eisen described some of the particular challenges facing Canada as it embarked on the development of a regulatory system for organs, tissues and cells used therapeutically. Canada is a vast country in size but with a relatively small population (approx 32 million) divided into 10 provinces and three territories, each with responsibility for the local management and delivery of health care. It is bordered on the south by the United States, with an exchange of tissues across the border in both directions. The complexity of the processes involved in organ, tissue and cell donation and transplantation is considerable, involving numerous organizations and stakeholders.

Health Canada is the federal authority regulating the safety, efficacy and quality of blood, cells, tissues and organs used in the country. Its goals in this field are to protect the people of Canada from current and emerging health threats from the therapeutic use of these products and to be on a par with, or exceed, regulatory programmes in other leading industrialized countries. In developing a new regulatory model, Health Canada aims to ensure a nationally-integrated approach with clear accountability and transparent working methods. They plan to harmonize internationally when possible, but also to identify areas where Canada should be a leader.

In Canada, food, drugs, medical devices and other therapeutic products including cells, tissues and organs are already regulated under the provisions of the Food and Drugs Act and Regulations. However, there are gaps in the current regulations and some of the product definitions, such as drug and device, present challenges to the regulation of cells, tissues and organs. Consequently, a new comprehensive framework will be implemented based on:

- Standards-based Regulations
- Surveillance
- Compliance and Enforcement

Health Canada aims to ensure that the framework balances high quality with the need to ensure availability.

Canadians expressed a clear demand for the development of national standards in this field via a number of national and parliamentary fora during the late 90s. Standards were considered to be the best vehicle for this type of regulation as they are developed with representative stakeholder input which is likely to enhance future compliance. Additionally, they are written in non-legal/regulatory language and are easier to update than regulations. In order for a standard to be recognized as a National Standard in Canada, it must:

- be developed through a consensus process;
- be developed by an accredited standards-writing body;
- be consistent with or incorporate existing international standards; and
- not be written to serve as a barrier to trade or to limit innovation or freedom.

In March 1996, an Expert Working Group was appointed by Health Canada to draft comprehensive Canadian standards. In March 2001, the standards were transferred to the Canadian Standards Association for further development and they were subsequently released as National Standards in August 2003. The scope of these standards covers the entire process from donation to transplantation; hence, federal, provincial and the practice of medicine responsibilities are impacted. They address aspects of safety for potential and actual donors and recipients, personnel and others and they serve as a benchmark and provide minimum requirements for verification of safe practices.

Standards are made mandatory only when they are incorporated directly or by reference into government regulations. A phased approach to the implementation of standard-based regulations is now under way.

Phase I will be implemented by 2005 and will comprise regulations based on:

- An establishment registration/attestation provision.
- The requirements in the CSA standards that fall under federal jurisdiction.
- Traceability and notification requirement.
- Mandatory reporting of certain adverse reactions to Health Canada.

Phase II will be implemented by 2006 and will comprise a comprehensive compliance and enforcement strategy and a comprehensive surveillance and adverse reaction reporting strategy, building on Phase I. Stakeholder consultation is already under way for this phase.

The regulation applies to cells, tissues and organs for allogenic use that are 'minimally manipulated' and that can be either viable or non-viable. It does not apply to cells, tissues and organs for autologous use, that are 'more than minimally manipulated' or that are used for assisted human reproduction. Blood and blood products are also excluded. It focuses on responsibility, stressing that source establishments are responsible for processing and distribution and for deeming the product suitable and safe for transplantation. The document is divided in sections including:

Interpretation Prohibition Registration Processing Donor Suitability Assessment Retrieval CTO Assessment CT preparation for use Quarantine Storage Packaging and Labelling	Exceptional Release Adverse Reaction Monitoring Records Personnel, Facilities, Equipment and Materials Quality Assurance System Transitional Provisions Coming into Force
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Until the new regulations are in place, Health Canada continues to regulate the safety of CTOs under the current framework and to address urgent safety issues as necessary. Canada, through its development of National Standards and the establishment of minimum safety requirements, is pleased to be able to contribute to the harmonization of global practices.

### **Key Points**

- Standards must be developed through an effective consensus process with wide stakeholder involvement
- For maximum impact, standards should be accredited by a legally recognized body and/or incorporated into binding regulations
- Adverse event reporting should be incorporated at an early stage in the implementation of regulations
- Standards must balance high quality with the need to ensure availability
- Standards and regulations must not limit innovation or serve as a barrier to trade

## **Session 2: Global Issues in CTTx**

Reports were provided by delegates from around the world, giving an overview of the current status of tissue and cell banking and transplantation in their countries and the role of various national and international professional organizations in support of this activity.

### **Tunisia**

Dr Mylène Ben Hamida explained that Tunisia has had national oversight since 1993 for the transplantation of cells, tissue and organs. The transplantation law bases donation on presumed consent unless the donor has signed the opposite on an identity card. There is a 65% family refusal rate for deceased donations, partly due to traditional refusal of mutilation of the body. Tissue bank activity is focused on the National Tissue Bank and is mainly for bone, amnion and cornea with imports of tissue from the US and France. There are no exports and there is a shortage of corneas. Tunisia identified a need for access to new technology for testing donors and enhanced training for tissue bank employees, as well as more education of the general population to increase donation rates.

### **Iran**

Dr Hamid R. Aghayan described a well-developed government-run oversight system for transplantation. Legislation was passed in 2000 and there is a donor registry for organ and tissue donation. The Iran Tissue Bank is the main bank that manufactures bone, heart valves and amnion. Procedures have been developed for processing that address safety issues through risk assessment. There are two cord blood and two bone marrow banks and over 15,000 volunteers in a haematopoietic stem cell registry. Iran does not import tissue and has a low rate of shortage for tissues. Heart valves are the only exported tissue. Dr Aghayan identified several challenges to meet future demand, including a sufficient budget to regularly inspect establishments, train staff and address accreditation by a professional association.

### **Pakistan**

Dr Abdul Majid Rajput reported that there is currently no tissue bank in Pakistan and, in particular, no cornea bank. The focus in Pakistan is on kidney transplantation. As in other Muslim countries the cultural background is against donation from deceased donors. There is a great need for education and government support to increase awareness for donation. A legal framework for transplantation that would include cadaveric donation is awaited.

### **India**

Dr Virender S. Sangwan indicated that most transplantation in India is for ocular repair. He reported that there is a registration system with 10 banks for amnion, 430 for cornea and eight for cord blood. Public awareness for donation is good for eye donation but not for other kinds of transplantation. There is a large unmet demand for tissues and organs, but no uniform standards (except for corneas), no compliance mechanisms or infrastructure and low governmental budgetary allocations for health.

## Sri Lanka

Dr Upali Mendis indicated that corneas are the main focus for transplantation in Sri Lanka. Over 2,000 transplantations occurred last year. Sri Lanka has also bone and fascia-lata banking and exports a lot of corneas to other countries in the region. There is no haematopoietic stem cell transplantation.

## Thailand

Dr Wirote Lausoontornsiri discussed Thailand's national oversight under the Ministry of Public Health. Thailand has only one or two banks for bone, skin, cord blood, heart valves, amnion and cornea. He identified increased demand for therapeutic CTTx as well as kidney and liver and a lack of public awareness for donation. Only haematopoietic stem cells are imported and bone is exported. Though there is some governmental oversight there is still a need for efficient, uniform regulation to assure safety. Issues identified for follow up were standardization for processing, tracking, efficacy review, follow up of donor and recipient and adverse effects. Of concern is access and the cost of CTTx because transplantation is not covered under national insurance.

## Australia

Dr Richard Allen described a well developed government oversight programme for cells and tissues that includes registration and inspection of facilities. The emphasis of the regulations is on prevention of transmission of infection. Twenty-three tissue banks were identified for bone, skin, cord blood, heart valves and cornea, as well as a large registry for donors of haematopoietic stem cells. No unmet demand for tissue was identified, though there is a shortage of kidneys. Thirty to forty percent of required haematopoietic stem cells are imported. Still in progress are requirements that will address oversight of tissue imports and exports.

## China

Dr Qi Guoming discussed an active network for the transplantation of haematopoietic stem cells, bone, skin, cornea, amnion and organs, though there is no national oversight for cadaveric tissue. Two bone banks have been approved by the government, but many others are operating. There is public support of donation, though the donation rates are low, even for those who have signed a donor card. Skin is imported from Holland and there are many transplantations for foreign patients willing to pay. There is a need for increase regulation to address registration or licensing and inspection. Concerns were raised about the quality and efficacy of transplants and possible abuse and unethical practices.

## Japan

Dr Tomonori Haegawa reported that there is little government oversight in Japan for cells and tissues except for bone marrow transplantation. Most oversight consists of voluntary compliance with medical societies' and associations' standards and is not uniform. There are several musculoskeletal banks and 22 cord blood banks, but most of the transplantation activity in Japan comes from 53 eye banks. Issues needing national implementation of oversight include registration, safety standards, inspections and surveillance. Another concern is to increase the rate of donation.

## Korea

Dr Suh Hosoo described extensive government oversight for cells, tissue and organ transplantation, including registration, licensing and the inspection of facilities and also indicated a significant number of bone, skin, amnion and cornea transplantations. There is a large donor registry for haematopoietic and bone marrow donors. He reported public support of donation, but there is still an unmet demand which requires importation. There are multiple cornea, amnion, cord blood and heart valve banks as well as 40 bone banks, though most of these are surgical bone banks located in hospitals. He expressed concern about unmet demand, the safety of imports and the need for a good tissue practice requirement.

## Argentina

Dr Carlos A. Soratti discussed a national system for oversight of cadaveric donation for organs and tissue including registration. He indicated that there was public support for donation, but a family refusal rate of over 50%. Argentina has multiple banks for bone, skin, cord blood, heart valves, amnion and cornea. There is a large registry for donation of haematopoietic stem cells and participation in the Bone Marrow Donor Worldwide Registry. Corneas and stem cells are imported and stem cells and occasionally heart valves are exported. The government is working on good tissue practice, quality assurance and surveillance requirements. Dr Soratti feels that worldwide exchange of tissues and cells is important.

## Brazil

Dr José Antônio de Faria Vilaça explained that cell and tissue transplantation in Brazil is focused on bone marrow, cornea and bone products with over 1,300 transplantations reported last year. There are multiple tissue banks that distribute bone, skin, heart valves, amnion and cornea as well as one cord blood bank and there is a large donor registry for haematopoietic stem cells. There is some government oversight but no registration, inspection or surveillance requirements to date. A large unmet demand was identified and a need for the development of quality standards to address safety concerns.

## Colombia

Dr Rafael Romero reported that there is national oversight for tissue and cell banks that include registration, inspection and surveillance. There is one bone, two skin, two heart valve and seven cornea banks registered in Columbia. Donation rates have increased in the past five years, but there is still a large unmet demand that needs to be addressed.

## Latin American Association of Tissue Banks

Dr Marisa Herson explained that many of the Central and South American tissue establishments are members of this organization, though there are some countries without any members. She indicated that it is difficult to determine how many banks are in Latin America because there is no common definition. The primary activity of this association is to motivate health authorities to prioritize regulations and inspection of tissue banking to assure safety. This association does not have standards for tissue establishments, but does encourage the utilization of those of other professional associations such as the American Association of Tissue Banks and also encourages uniformity between countries. The association is also active

in promoting activities that will increase the rates of donation and educate donors. A 90% unmet need in Latin America was quoted.

### Eye Bank Association of America

Dr Ellen Heck explained that the EBAA consists of 85 accredited and three non-accredited US eye banks and 16 international banks that distributed over 49,000 corneas last year. Over 14,000 of the US corneas were exported to various countries to assist with their unmet need. The mission of the association is to provide the safest possible quality tissues for transplantation, to enhance supply to match needs and availability, as well as to provide opportunities for research and education. To ensure this the EBAA has published medical standards that their accredited banks must adhere to.

### American Association of Tissue Banks

Mr Scott A. Brubaker explained that the association's mission is to facilitate the provision of safe, transplantable tissue of uniform high quality in quantities sufficient to meet national needs. To accomplish this the AATB, founded in 1976, maintains standards that help to prevent disease transmission and ensure optimal clinical performance of transplanted cells and tissues. These standards are updated periodically and provide detailed requirements from retrieval to distribution. The Model Element of Informed Consent is also included. Establishments are accredited after a thorough review and inspection and are subjected to a 3-year re-inspection cycle. AATB also provides training and certification of tissue banking personnel and promotes education focused on quality and safety. Currently there are 86 accredited musculoskeletal, cardiac/vascular, skin and reproductive banks in the US and Canada. Based on a 2002 survey of accredited banks with 59 banks reporting, tissue was recovered from over 23,000 donors and distributed in the US and to 39 other countries.

### United States

Ms Jill Hartzler Warner (with the assistance of Ms Martha Wells) reported that there were over one million tissue transplants last year in the US and this number is increasing. The actual transplantation of the tissue or cells by a physician is regulated by the states through licensing of medical practitioners and is not directly regulated by the federal government. In contrast, the Food and Drug Administration (FDA) regulations, with a focus on the article or product, apply to cells and tissues, include haematopoietic stem cells and reproductive cells and tissues and address recovery of the tissues from the donor to distribution for transplantation. There is comprehensive government oversight that includes registration of facilities, inspection and surveillance. Government oversight is focused on the prevention of transmission of communicable disease and includes specific donor eligibility requirements. Over 1,200 cell and tissue establishments are registered with the FDA. Donor registries for haematopoietic stem cells list over four million potential donors. The FDA recognizes the need to balance safety oversight of haematopoietic stem cell imports with the critical needs of patients. FDA is streamlining its administrative processes to facilitate rapid access to time-sensitive products. Concerns remain over making the best use of limited resources for maximum impact on public health and development of the appropriate level of oversight for haematopoietic stem cell products.

## Canada

Ms Liz Anne Gillham-Eisen explained that Canada is in the process of developing and implementing regulations for tissues and cells that will include registration, inspection and surveillance. Standards have been developed that are the basis of the requirements for organs, tissues, cells and gametes. There is public support for donation with over 88% indicating that they are willing to donate though there is unmet demand that makes importation necessary. Over 100% of dental bone tissue and 70% of other tissues is imported. There are approximately 645 tissue establishments and 35 cell programmes. Over 4,000 deceased donors and 1,600 live bone donors were procured last year. Concerns with increasing donation rates and oversight of imported tissue were mentioned.

## Nigeria

Dr Bappa Adamu explained that there is no cell or tissue transplantation or donation in Nigeria at this time. There is no government infrastructure, support for donation or payment for transplantation. A small number of kidney transplantations have been carried out both in private and in public sector but activity remains limited. Besides having a high unmet demand there is high mortality of those in need of transplants.

## Council of Europe

Ms Alina Tatarenko gave an overview of the role of the Council of Europe in setting ethical and technical guidelines for organ, tissue and cell banking and transplantation. The Council of Europe has a membership of 46 states in Europe, representing over 800 million Europeans. It has specialist committees on the organizational aspects of organ transplantation (SP-CTO) and an expert group which works on quality assurance for organs, tissues and cells (SP-SQA). It is also undertaking a research study on cellular immune therapies (SP-CIT).

The work of the Council of Europe in the field of substances of human origin is based on a number of key principles, as follows:

- Non-commercialization.
- Voluntary, non-paid donation.
- Self-sufficiency.
- Protection of donors and recipients.

Its objectives are to study ethical, legal and organizational aspects of the field to ensure quality and availability, to avoid wastage by ensuring optimal use and to examine the potential ethical and organizational impact of new scientific developments.

In 1997 the Council of Europe published the Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine. In January 2002 an Additional Protocol on transplantation of organs and tissues of human origin was opened for signature. A number of Recommendations have been agreed and published in the field of transplantation, including a number concerning organ transplantation, one on autologous cord blood banks and one on xenotransplantation. The Council of Europe organizes a European Day for Organ Donation and Transplantation each year to promote awareness of donation in Europe. It also provides assistance to Member States, geared to their specific needs, which can include seminars and task force missions.

A Guide to Safety and Quality Assurance for Organs, Tissues and Cells has been produced by the Council of Europe and is now in its second edition (September 2004). This covers all aspects of the process from donation to transplantation. The guidance is not mandatory but Member States may incorporate it into their national regulatory framework.

## European Union

Dr Bernard Loty, on behalf of Dr Eduardo Fernandez of the European Commission, outlined the activities of the European Union (EU) in the regulation of tissue and cell donation and supply. The EU currently has 25 Member States. Its legal basis is a series of European Community and, more recently, European Union treaties, currently the Treaty of Nice. European legislation agreed by the EU binds Member States which must transpose it into their own legislation within agreed timescales. The legal basis for EU law on substances of human origin is:

Article 152 on the subject of public health. It aims to protect health by setting minimum standards. An example of a directive adopted on this legal basis is the Blood Directive. Article 95 relates to the internal market in the EU and has the objective of allowing free circulation and harmonization. An example of a directive adopted under this legal basis is the Medicinal Products Directive.

Article 152 states that the EU "...Shall contribute to the achievement of the objectives referred to in this Articles through adopting:

(a) Measures setting high standards of quality and safety of organs and substances of human origin, blood and blood derivatives. These measures will not prevent any Member States from maintaining or introducing more stringent protective measures."

Article 152 therefore allows the establishment of binding standards to all issues related to quality and safety of organs, blood and substances of human origin but not to non-safety issues, such as ethics. Harmonization is not ensured by Article 152 and it does not affect Member State responsibilities for the organization of organ, tissue or blood donation or banking.

The Tissue and Cell Directive (2004/23/EC) was adopted in April 2004. All Member States must comply by April 2006. This directive addresses issues such as the need for inspection and accreditation of tissue establishments, for traceability and a European coding system and for European surveillance. Two further supporting directives are now under development through the 'comitology' procedure. These will provide more detailed requirements. The first will address donation, testing and procurement. The second will address processing, storage, distribution and traceability. These will also represent legal requirements but it will be possible to update them more quickly than the main directive.

## France

Dr Bernard Loty described an extensive system of tissue banks and comprehensive regulations that are in place in France. These regulations cover donor protection, procurement, safety, inspection and surveillance. When regulations were implemented in 1994 there were 226 tissue banks whereas now there are only 43 authorized tissue banks. In 2003 over 20,000 tissue and over 4,000 haematopoietic stem cell transplantations took place. France has a large donor registry for haematopoietic stem cell donation that is rapidly growing. There is a recognized unmet demand for corneas.

## Germany

Dr Thomas Hinz reported comprehensive governmental oversight of all stages of tissue and cell transplantation products. This includes registration, inspection, surveillance and licensing of tissue-engineered products. He listed 300 bone, two skin, three cord blood, five heart valve, 10 amnion and 21 cornea related establishments and reported over 200,000 transplantations per year. Germany also reports wide public support for donation and a haematopoietic stem cell registry of over two million potential donors. However, there is concern for unmet demand and the need to address quality and safety concerns.

## Italy

Dr Deirdre Fehily reported that the mission of the National Transplant Centre established by law in 1999 is to promote, coordinate and direct organ and tissue donation and transplantation activity in Italy. Italy has excellent interregional, regional and local coordination of these activities, built on a well developed organ donation programme with the second highest donation rate per million population in Europe. There are many tissue banks including six bone, five skin, five heart valves, 15 cornea, 14 cord blood and a haematopoietic stem cell registry with over 309,000 potential donors registered. Cornea banking is particularly well developed with 5,518 corneas distributed in 2003. Oversight includes tissue-specific standards, inspection and surveillance of recipients of stem cell transplants. A vigilance system to address adverse events in tissue transplantation is under development. Concerns were raised regarding possible unauthorized imports, as well as problems with accurate testing of cadaveric blood.

## United Kingdom

Dr George Galea described government oversight that is in development and being driven by recent EU directives for tissue banking. A transplant authority is being formed. There is a wide range of tissue banks in the UK including 32 bone, three skin, three cord blood, six heart valve and two cornea, as well as over 640,000 donors registered as haematopoietic stem cell volunteers. Third parties provide accreditation of tissue establishments and government inspection is voluntary. Concerns were raised over unmet demand and safety concerns for vCJD transmission.

## The Netherlands

Dr Arlinke G. Bokhorst explained that there is governmental oversight that licenses centrally organized foundations to oversee tissue transplantation. There are requirements for processing, storage, packaging, release and distribution. The national transplantation authority oversees registration, inspection and surveillance of recipients. There is also a large voluntary central registry that citizens can opt into with over five million potential donors. She reported that there are six bone, one skin, two cord blood, one heart valve and amnion and two cornea banks in the Netherlands. A shortage of heart valves and certain sizes of bone was identified. Safety concerns were raised for donor testing and emerging infections. Future challenges include implementing EU directives, balancing demand and supply and improving yield while lowering costs.

## Slovakia

Dr Jan Koller reported good oversight based on law for tissues. Oversight includes a national transplantation authority, registration, inspection, surveillance of recipients and vigilance on adverse effects. There are two multi-tissue banks that distribute bone, skin, heart valves and amnion. There is one cord blood bank and a small registry of 500 volunteers for haematopoietic stem cells. Only corneas are exported regularly and unmet demand has not been specified. Concern was raised about insufficient reimbursement for transplantation and for safety of the tissues distributed.

## European Association of Tissue Banks

The purpose of the European Association of Tissue Banks (EATB) is. "To promote science, research and teaching in the field of tissue banking and related sciences, both in Europe and more widely, and to publish safety and quality standards for Tissue Banking."

The EATB is an association of tissue banking scientists and professionals which was founded in 1991 and has its secretariat in Berlin. It produces the journal *Cell and Tissue Banking* published by Springer. It has an executive committee and a Board of Councils and Committees and it holds a General Meeting of its members every two years. It had 210 active members in 2004 and holds a scientific meeting each year. As an association, it collaborates with other professional organizations such as the European Association for Transplantation (EAMST) and the European Eye Banking Association (EEBA). The EATB plays an active role in advising the Council of Europe, the European Union, WHO and the International Atomic Energy Agency (IAEA). It also collaborates with partner organizations outside Europe such as the American, Asian Pacific and Latin American tissue banking associations.

The EATB first issued its General Standards in 1994 and an update on these in 2003. An Ethical Code was also published in 1994. It has tissue-specific standards for skin, reproductive cells, eyes, tissues and heart valves.

### **Key Points**

- Many countries have poorly developed access to essential CTTx (e.g. cornea)
- Many countries lack regulatory frameworks for CTTx
- At national level in most countries CTTx activity data is not available, hampering the development of regulatory oversight
- There is a significant degree of international circulation of CTTx, a large fraction of which occurs outside of any regulatory oversight
- The considerable experience of regulating CTTx banking activities in some developed countries provides invaluable guidance to other countries as they embark on this task
- Professional societies play an essential role in the agreement of requirements and best practices which can be used as the platform for the development of legally binding regulations

## **US Regulatory Oversight and Surveillance of Human Cells and Tissues**

Ms Jill Hartzler Warner, J.D., provided an overview of the US Food and Drug Administration's (FDA) approach to the regulation of human cells and tissues and the challenges in developing the new approach. The FDA developed a comprehensive, risk-based regulatory framework in response to increasing concerns involving the transmission of communicable disease via cells and tissues, the rapid increase in numbers of transplants and the growth in new technologies for cell and tissue-based therapies. Public expectation for tissue safety is high, as many procedures utilizing tissues are life enhancing rather than life saving. Over 100 transplants may be derived from a single donor, so many patients are at risk if tissues do not meet safety criteria. While infectious disease testing is important, tests are not always available for all agents of concern and they are not foolproof. Industry standards are also useful but they are not universally followed and are not enforceable. The demand for tissue and cellular products is likely to increase and the perception of a poorly regulated industry could thwart tremendous technological promise.

The FDA has regulated tissues since 1993. However, the FDA's overall approach to the regulation of tissues and similar products was fragmented. Tissue and cell-based products did not always fit existing regulatory 'pigeon holes'. The FDA provided strict criteria for the regulation of some products, such as cell-based gene therapies, whereas some tissues and cells were not actively regulated, such as haematopoietic stem cells. Although the 1993 tissue regulations applied to tissue, those regulations focused primarily on hepatitis and HIV and did not comprehensively address many of the safety concerns increasingly being identified.

In developing the new approach, a number of factors influenced its scope. First, the FDA relied on existing statutory authorities. The new regulations for human cells, tissues and cellular and tissue-based products (HCT/Ps) rely on section 361 of the Public Health Service Act, which authorizes regulations to prevent the introduction, transmission and spread of communicable diseases. Because organs and bone marrow are within the purview of a different US agency, they were excluded from the FDA's framework. The framework also does not include blood, blood products and xenotransplantation products. Other challenges included tackling previously unregulated products (such as haematopoietic stem cells), addressing therapies that often raise complex social and policy issues (such as cloning, embryonic stem cells and assisted reproductive technologies) and the reality of limited resources.

The FDA announced its proposed approach to the regulation of cell and tissue products in February 1997. The framework is risk-based and includes a broad range of products – tissue, ocular tissue, cellular therapies, haematopoietic stem cells, reproductive tissue, combination products, human heart valve allografts and dura mater. The FDA incorporated a number of principles into the framework: the level and type of regulation should be commensurate with risk, like products should be treated alike and the FDA should exercise regulatory oversight only to the degree appropriate to protect public health. The regulatory framework has three main goals:

1. To prevent the unwitting use of contaminated tissues with the potential for transmitting infectious disease.
2. To prevent improper handling or processing that might contaminate or damage tissues.

3. To require demonstration of clinical safety and effectiveness for most tissues that are highly processed, are used for non-native purposes, are combined with non-tissue components or that have systemic effects on the body.

The FDA has promulgated new regulations to implement the proposed approach. The new regulations require establishment registration and product listing, donor screening and testing, good tissue practice and adverse reaction and product deviation reporting and will be fully effective in May 2005. Establishments are required to register with the FDA and provide a list of their HCT/Ps; however, registration does not connote licensure or approval.

Donor eligibility consists of screening donors and testing blood samples for relevant communicable diseases. FDA regulations identify HIV 1 and 2, HBV, HCV, CJD and *Treponema pallidum* as relevant communicable diseases for all HCT/Ps and HTLV I and II as relevant communicable diseases for viable, leukocyte-rich HCT/Ps. The regulations facilitate identification of new relevant communicable diseases if the disease meets specified criteria: there is a risk of transmission via HCT/Ps, the disease can pose a significant health risk and appropriate screening measures and/or a screening tests are available.

Good tissue practice includes the methods, facilities and controls for manufacturing to prevent infectious disease contamination. The regulations set out broad goals applicable to the wide range of HCT/Ps covered by the regulations and establishments have the flexibility to determine how to meet the goals through setting their own procedures. Good tissue practice requires a quality programme to prevent, detect and correct deficiencies that could increase communicable disease risk.

The regulations require that HCT/Ps be recovered, processed, stored, labelled, packaged and distributed and that donors be screening and tested to prevent the introduction, transmission and spread of communicable diseases. The regulations require that HCT/Ps be tracked and that adverse reactions and HCT/P deviations be reported to the FDA.

Ms Warner identified several advantages of the FDA's approach, including a unified, comprehensive framework, consistency with industry standards, support and input from industry and the public, a mechanism to rapidly address new, emerging agents of concern and the risk-based approach that provides a platform of minimum requirements applicable to all cells and tissues, with additional requirements added where necessary for safety and effectiveness. She also noted challenges and priorities, including the need to leverage limited resources for maximum impact on public health and the need to rapidly detect, analyse and respond to adverse reactions.

**Key Points**

- The US has recognized, since 1993, that regulation of tissue and cell banking is essential for patient protection
- The perception of a poorly regulated industry could thwart tremendous technological promise
- US experience shows that implementation of regulation is an iterative process involving feedback of adverse event information to drive improvement
- Regulations in the field must address quality and safety in both the public and commercial settings where priorities and context can vary considerably

## **Session 3: Safety and Surveillance in CTTx**

### **Cells, Tissues, and Organs Used in Transplantation: Adverse Event Monitoring and Surveillance System**

Dr Tony Giulivi described Canada's approach to adverse event monitoring and surveillance activities relating to cells, tissues and organs. The Public Health Agency of Canada performs public health surveillance, while the Health Products and Food Branch of Health Canada conducts product safety surveillance. Dr Giulivi defined surveillance as the tracking and forecasting of health events through the systematic collection, analysis and interpretation into surveillance products. The surveillance products must then be made available in a timely fashion to decision makers and surveillance systems must be able to respond quickly to change.

Dr Giulivi described the model that Canada has used for risk assessment of emerging bloodborne pathogens. The system relies on a number of health care facility-based disease and surveillance networks, including the cell, tissue and organ transplant surveillance network.

Canada is currently considering regulatory requirements for reporting errors and accidents, immediate reporting of certain adverse events, traceability of products and monitoring and surveillance. Other issues under consideration include the problem of under-reporting of adverse events and the 'who, what, when and how' of adverse event reporting.

Blood and marrow programme surveillance is conducted in Canada with the goal of carrying out surveillance and targeted research leading to risk assessment of transfusion-related bloodborne pathogens and injuries. Health Canada and the Canadian Blood and Marrow Transplant Group jointly coordinate a registry. The objective of the registry is to monitor the incidence of emerging bloodborne pathogens in special groups, including those who are immuno-compromised or receive multiple transfusions. Data from the registry will be used for disease surveillance and to support clinical research and decision-making. The data elements in the registry include demographical information, diagnoses, treatment history, bone marrow and cell therapy, blood transfusion history, documented infections and emerging syndromes.

Dr Giulivi emphasized that Health Canada and the Public Health Agency of Canada are responsible for product safety and public health surveillance respectively, but collaborate on these issues. The Cell, Tissue, and Organ Surveillance System will be an active surveillance system aimed at enhancing the existing passive surveillance system for adverse event monitoring.

Dr Giulivi outlined the key new elements of the public health response in Canada. These include:

- The Public Health Agency of Canada with two pillars: Winnipeg (headquarters) and Ottawa.
- The Pan-Canadian Public Health Network.
- Public Health Goals developed by the Ministers and Pan-Canadian Public Health Strategy.

- Six National Collaboration Centres for public health.
- Enhanced international collaboration

Canada plans to develop a strategic approach to international activity. Strategic linkages and activities with key international partners will support improved outbreak response, emergency preparedness, surveillance and capacity building and information sharing.

### **The New US Adverse Event Monitoring System**

Ms Martha Wells, United States FDA, provided additional information on the US plans to implement requirements for adverse reaction and product deviation reporting for human tissues in 2005. These requirements, as well as the requirement to register establishments and list products with the FDA, apply to all US establishments and to foreign establishments that distribute CTTx to the United States. These establishments will be required to keep a complaint file on any distributed CTTx concerning any communication related to a transmitted or potential transmission of a communicable disease. Establishments will also have to investigate all adverse reactions involving a communicable disease reported to them and report to the FDA using Medwatch Form FDA 3500A within 15 days if it is fatal, life-threatening, results in permanent damage or necessitates medical or surgical intervention. Deviations that are required to be reported to FDA by the establishment distributing the CTTx using FDA Form 3486 include unexpected or unforeseeable events in the manufacture of the product that may be related to the transmission or potential transmission of a communicable disease or may lead to such contamination. These may be discovered during an investigation of a complaint.

Ms Wells emphasized the importance of informing clinicians in other countries using US distributed CTTx that they need to report possible adverse reactions to the manufacturer and to voluntarily report to the FDA using the Medwatch FDA Form 3500. These forms and access to the Biological Deviations Data Base to report online can be found at <http://www.fda.gov/cber/biodev/biodev.htm>.

#### **Key Points**

- Surveillance is an essential tool for the development of transplantation strategies and policies
- Surveillance should be active and comprehensive, not limited only to adverse event reporting
- Effective surveillance requires the active collaboration of clinicians, operators, regulators and health authorities
- Effective surveillance requires international collaboration, both in relation to tissues that are distributed globally and to the need for wide dissemination of risk information

### **Towards a Global Knowledge Database on Risks and Safety Measures for Infections Associated with Human Material for Therapeutic Use**

Dr Silvano Wendel discussed the realities that must be taken into account in developing a global database on cell and tissue transplantation and emphasized the importance of working towards the goal of creating a global database.

Human cell and tissue transplantation is a complex process involving technical, legal and ethical aspects. It is important to be cognisant of the worldwide disparity regarding the level of human development – including life expectancy, education and standard of living. Moreover, local, regional and national epidemiological patterns must be recognized since not all infectious agents are ubiquitous. Issues such as the voluntariness of donations, the disequilibrium created by demand exceeding supply, cultural and religious issues, population, allogeneic vs. xenogeneic transplants and living vs. cadaveric donors contribute to the complexity of cell and tissue transplantation worldwide.

Dr Wendel presented data showing the distribution of infectious disease, including hepatitis B and C, HIV, dengue fever, yellow fever, Japanese encephalitis, West Nile virus, malaria, Chagas disease and tuberculosis. He stressed that a foundation of technical, legal and ethical guidelines, traceability of cells and tissues, cell and tissue vigilance and accountability are necessary to support a global database.

Dr Wendel described the European Haemovigilance Network, which has proposed defining cell and tissue vigilance as “a set of surveillance procedures covering the whole transplant chain (from the potential organ candidate to the follow up of recipients), intended to collect and assess information on unexpected or undesirable effects resulting from the transplantation of human cells, tissues or organs and to prevent their occurrence or recurrence”.

Dr Wendel proposed that creating a global database is achievable through a multinational epidemiological stepwise exercise. Such a database should have central coordination, periodic reports, space and time comparison and credibility. Credibility can be established by ensuring that accredited bodies complete questionnaires, requiring peer review of reports, recognizing all institutions and banning smoothing factors on reports. The database should be freely accessible to all and can support the global development of transplants.

Dr Wendel stressed the importance of the application of a global numbering system for tissues and cells to provide security to traceability systems.

### **Key Points**

- A global knowledge database on transplantation (GKT) practices, safety, quality, efficacy, epidemiology and ethical issues, including living donation is requested by resolution WHA 57.18
- Activities reported should include procurement, production and use of CTTx
- GKT will facilitate transplantation risk assessment by providing reference information and surveillance data globally
- Credibility of GKT is essential and the reliability of data will depend on ongoing international networking of national regulatory authorities and operators as well as public transparency
- Existing national and regional experience in surveillance of therapeutic products of human origin should be consolidated, shared and expanded towards encompassing global activity

## **Discussion and Summary of Day 1**

There was a general consensus on the need to enhance the safety and availability of cell and tissue transplantation. From a global perspective, a wide variation on the scale and nature of activity exists among countries. There is a need for increased consistency in characterizing types of transplants; for example, comparing transplants of skin proves difficult given that a 'unit' may be measured per transplant or per square foot. Moreover, significant gaps in information, including data on activity and outcomes, and import/export activity, exist. The level of regulation of transplant activity varies from stringent regulation to little or even no regulation. Effective regulation must be cognisant of the process of transplantation as well as the products involved in transplantation.

Participants noted that priorities in enhancing the safety and availability of cell and tissue transplants should include addressing the risk of infectious disease transmission, supporting educational efforts to increase rates of donation and effective transplantation and developing traceability and vigilance capability among countries.

## **Session 4: CTTx: Essentials for Good Practice, Governance and Oversight**

### **The Role of National Health Authorities in Ensuring Access to Safe, Effective and Quality Tissues and Cells: The French Experience**

Dr Bernard Loty provided an overview of the history of the development of regulation in France. Early laws regulated the fields of cornea and organ retrieval (1949 and 1976 respectively), the latter requiring explicit consent for living donation and introducing presumed consent for deceased donation. The Bioethical Acts of 1994, revised in 2004, covered all aspects of organ, tissue and cell procurement, banking supply and implantation. Other relevant laws include the Cell and Gene Therapy Law of 1996, the Public Health Safety Law of 1998 and the Customs Law of 1992, revised in 1998.

French regulation has been developed on the platform of two national agencies: the French Transplantation Agency (EFG), created in 1994, and the Health Products Safety Agency (AfSSaPS), created in 1998. It includes provision for:

- Donor Protection.
- Procurement Regulation (authorization and inspection):  
With the advice of the EFG, regional agencies inspect and authorize hospitals to carry out the retrieval of organs and tissues for therapeutic purposes (surgical residues are excluded). Aspects evaluated include the procurement coordination team, the general organization, facilities and equipment and traceability. Standards for procurement are set nationally. Over 200 centres are authorized for procurement.

- Safety (donor selection, traceability, adverse reaction management): Donor selection must rely on medical history including CJD risk factors and minimum donor testing (to include HIV 1 and 2, HTLV 1, hepatitis B and C and syphilis; p24 or NAT also required for HIV and HCV; additional tests are required for cell donation).
- Banking Regulation (authorization and inspection): Inspection of tissue banks is against national quality standards agreed for processing, preservation and storage and on national distribution rules. There is inspection and authorization for each type of tissue, for each facility and for each process. ‘For profit’ banks can be authorized if high technology is involved. A 2003 decree requires adverse event reporting. There are specific rules for cell banking authorization. Process or product authorization requires presentation of the results of preclinical studies and clinical trials. There is also a requirement for the authorization of clinical trials.
- Importation Authorization.
- Transplantation Rules (waiting list management, allocation, authorization).

During the period when regulation was being developed, the number of tissue banks operating in France reduced from 226 in 1993 to 43 authorized banks in 2004 (see Figure 1). This reflected the closure of a large number of small banks run within surgical departments, where it was not possible or cost-effective to raise standards adequately to ensure compliance with the national requirements.

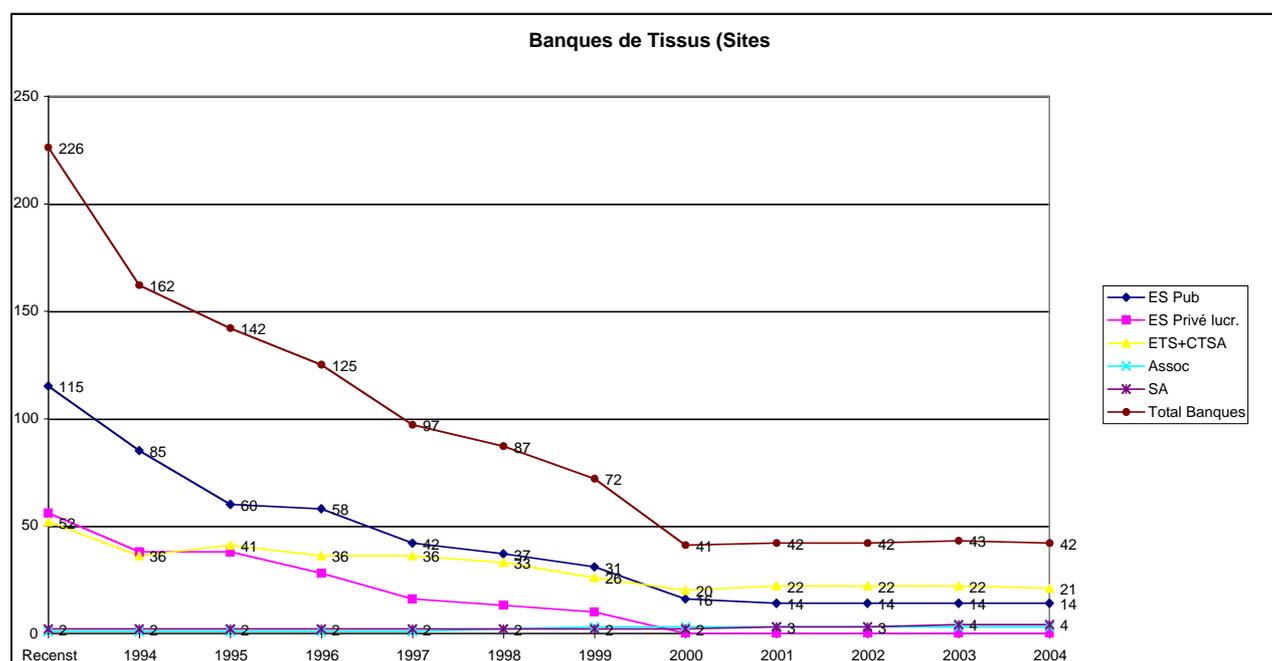


Figure 1: Evolution of the number of tissue banks in France during the last decade

Apart from one or two areas where skin banking should be developed, there is now a good provision of services geographically. During this same period, the supply of tissues was increased for all tissue types, despite the reduction in the number of banks.

Dr Loty stressed the need for the benefits of transplantation to be considered and weighed against the risks when developing donor selection rules. In many cases tissues and organs are life-saving and the risks of not providing a transplant must be included in the assessment. He reported that during 2002 a total of 282 organs were lost due to the testing rules while 490 patients on the waiting list were positive for hepatitis B or C. Many organs, tissues and cells were lost and importation was paralysed between 1992 and 1997 when HTLV 2 as well as HTLV 1 testing was required, due to a high rate of false positivity and indeterminate results. This was in a context of very rare infection with HTLV 2 in France, unknown pathology associated with the virus and an unknown transmission risk. The need to avoid over-regulation which reduces the availability of tissues and cells without adding equivalent safety was highlighted.

### **Key Points**

- The development of regulation and planning for CTTx services is the responsibility of the national health authority
- It has been an iterative process based on experience that should be used by countries now developing their CTTx services
- The legal framework should provide for the protection of the donor as well as the optimal outcome for the recipient
- It should address tissue establishment authorization and inspection, oversight of importation and transplantation rules
- Implementation of quality and safety requirements led to the closure of many CTTx establishments that could not comply due to their limited resources
- The organization of tissue and cell banks should result in concentration of activities to facilitate the effective implementation of quality systems while ensuring adequate patient access and in a geographically planned manner

## **Essential Process Requirements for Cell and Tissue Transplantation from Procurement to Follow up of Recipients**

Dr Yeowon Sohn reviewed the current safety and quality system requirements for tissues and cells from an international perspective. The context is one of increasing clinical demand for tissues and cells for transplantation, emerging technologies for processing and manipulation and accelerated development of new products such as stem cells and 'tissue-engineered' products. There are a number of challenges in this field including increasing public health concern and a very high public expectation for safe and effective products. The increasing scale of international exchanges of cell and tissue products bring additional risks.

There is a wide range of human-derived products included in the tissue and cell category, including the following examples:

- tissue
- ocular tissue
- dura mater
- human heart valves
- reproductive tissue

- haematopoietic stem cells
- cellular therapies
- manipulated cells and tissue
- genetically modified cells
- tissue/cells combined with devices, biologics or drugs.

This group of products includes tissues and cells with widely varying characteristics and associated risks: autologous vs. allogeneic, viable vs. non-viable, banked vs. unbanked, homologous vs. non-homologous function, 'minimal' vs. 'more than minimal' manipulation, structural vs. systemic function when implanted and single cell/tissue product vs. combination product (device, biologic or drug).

In the US these products are regulated under the Food, Drug and Cosmetic Act and/or section 351 of the Public Health Service Act if they are 'more-than minimally manipulated', used for a non-homologous or a metabolic function or combined with non-tissue/non-cellular components. If, on the other hand, they are only 'minimally manipulated', they are used for a homologous, non-metabolic function and they are not combined with a drug or device, they are regulated under section 361 of the Public Health Service Act.

The major areas of regulatory concern for tissues and cells are in the prevention of the use of contaminated tissue that can transmit infectious disease, the prevention of improper handling/processing that might contaminate or damage tissue and the demonstration of clinical safety and efficacy, where appropriate. For somatic cell therapies and combination products there are further considerations such as potential toxicity, the need for product characterization and testing and for process consistency and validation.

To prevent the introduction, transmission and spread of communicable diseases by these products the US applies 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 key elements included in the GTP rules come under the following headings:

- Quality programme
- Organization and personnel
- Procedures
- Facilities, environmental control and monitoring, equipment and supplies and reagents
- Processing
- Labelling controls
- Storage
- Receipt and distribution
- Records
- Tracking
- Complaints file.

These are similar to the areas covered by 'Good Manufacturing Practice' (GMP) regulations:

- Organization and personnel
- Buildings and facilities
- Procedures
- Equipment
- Control of components and drug product containers and closures
- Production and process controls
- Packaging and labelling controls
- Holding and distribution
- Laboratory controls
- Records and reports.

Quality must start at donation and continue through procurement, processing and storage to distribution. The European Union (EU) is setting up the regulation of donor selection and evaluation requiring donations to be voluntary and unpaid. It also regulates for the protection of donor and recipient data and confidentiality. It requires full documentation of donor evaluation and testing.

Awaiting formulation of EU mandatory requirements, current recommendations from the Council of Europe require testing for:

- ✓ HIV 1 and 2
- ✓ Hepatitis B
- ✓ Hepatitis C
- ✓ *Treponema pallidum*
- ✓ HTLV I and II in donors living in and coming from high incidence areas.

In order to reduce the risk and maximize the benefits of the transplantation process, it is necessary to operate an effective quality management system (QMS) to include the following key elements:

– Personnel and organization:

Staff should be appropriately qualified and their tasks and responsibilities should be clearly understood and documented (usually in an organizational chart). Key personnel should include a responsible person (RP), an independent head of quality assurance (QA manager) and a medical specialist/adviser. Training requirements should be documented and training records maintained.

– Premises, equipment and materials:

Premises and equipment must be designed, located, constructed, adapted and maintained to suit the operations to be carried out. There should be dedicated secure and monitored areas for storage of the different categories of cell and tissues. Storage conditions should be controlled, monitored and checked. Maintenance, monitoring, cleaning and calibration of equipment should be documented and records kept.

– Detailed specifications for the purchase of reagents are required.

- Documentation:  
Documentation ensures that work is standardized and that there is traceability in all steps. It should include a Quality Manual; specifications for materials, labels, equipment, tissues, cells and reagents; Standard Operating Procedures (SOPs); records on the performance of operations; protocols for audits and the management of complaints and training and competency records for personnel.
- Selection, procurement, testing and processing/handling:  
Policies and procedures for the safe selection and testing of donors need to be in place. Tissue and cell procurement should be carefully controlled. Defects that may adversely affect quality must be documented and dealt with. Facilities must have adequate systems of process control and environments must be adequately controlled. When a microbial inactivation procedure is applied to the tissues or cells it must be specified, documented and validated. Before new processes are implemented, they must be validated.
- Quality control and proficiency testing:  
Quality control comprises those activities that ensure that materials and processes meet the required specifications. There should be internal quality control and, where relevant, external quality assessment (proficiency testing).
- Traceability:  
There needs to be a system that enables the path followed by each donation to be traced, from the donor to recipient(s) or to disposal.
- Complaints, errors and accidents, adverse events and recalls:  
All complaints, errors, accidents and adverse events must be investigated and documented and appropriate corrective and preventive actions taken.
- Self assessment, internal audit and external audit:  
There should be a system of internal and external audit which allows for continuous improvement.
- Tissue and cell storage conditions:  
Storage conditions, including relevant or critical parameters such as temperature, humidity and sterility, must be defined, controlled, monitored and recorded. A maximum storage time must be specified for each type of storage condition.
- Distribution:  
Transport parameters, such as temperature, must be defined to maintain the required tissue and cell properties. Packaging must ensure that the tissue is maintained in the condition established in the Standard Operating Procedures.
- Final labelling for distribution:  
Every unit of tissues/cells must be labelled with at least:
  - Identification number, or code of the tissues/cells
  - Characteristics of tissues or cells
  - Identification of the tissue bank
  - Lot number.

When tissues/cells are distributed certain information should be provided in the accompanying documentation:

- Morphology and functional data
  - Date of distribution of tissues/cells
  - Serological determination carried out on the donor and the results
  - Storage recommendations
  - Instructions for opening the container/package
  - Expiry date after opening/manipulation
  - Instructions on reporting serious adverse reaction and/or events.
- External labelling of the shipping container:  
The external shipping container should be labelled with the identification of the originating tissue bank, the identification of the health-care establishment of destination, a statement that the package contains human tissues/cells, recommended transport conditions and safety instructions.

Dr Sohn summarized the current arrangements for the regulation of cells and tissues in Korea. Certain products, including tissues, skin and heart valves, are regulated as human tissue under the Human Tissue Safety and Control Act. Cellular therapies, manipulated tissue and cells, genetically modified cells and tissues or cells combined with a device, biologic or drug, are regulated as biologics under the Pharmaceutical Affairs Act. There are currently many cell therapy products in the NDA and IND stages of regulation and a long list of cell products in the pre-IND stage including fibroblasts, osteoblasts, myoblasts, mesenchymal stem cells, pancreatic islets and cord blood stem cells.

## **Session 4: Discussion**

During a wide-ranging discussion, many delegates expressed support for the development of a WHO Aide Mémoire addressing Governance, Oversight and Good Practice in tissue and cell procurement, banking and distribution. This proposal was particularly supported by experts from developing countries where little or no regulatory infrastructure is in place for this activity. It was stressed that a WHO document would carry considerable authority and would stimulate positive action.

The Aide Mémoire would have two main sections: the first providing guidance to Member States on the need for national oversight, to include standard setting, registration, inspection, authorization and surveillance, the second section would address the key principles of good practice and quality assurance that should be applied when human tissues or cells are donated, processed, stored, distributed and transplanted. It was confirmed that such an Aide Mémoire would not require approval by a WHO expert committee such as the Expert Committee on Biological Safety (ECBS). Dr Noël supported this proposal and agreed to take it forward.

### **Key points**

- There needs to be national regulation of tissue and cell transplantation activities to ensure patient safety and clinical efficacy
- A comprehensive quality management system must control the process from donor selection to clinical outcome
- There are well developed and tested quality systems (e.g. Good Manufacturing Practice, ISO quality system standards) applicable to tissue and cell banking which must be thoroughly and consistently implemented
- All elements of quality systems are relevant to tissue and cell banking, particularly those that assure traceability, adequate documentation and adverse event reporting and investigation

## **Session 5: Cross-cutting Specifications for Cells and Tissues for Transplantation**

### **Normative Work at WHO**

Dr David Wood described the system for developing and approving standards within WHO. WHO is mandated by its 192 Member States to "...develop, establish and promote international standards for biologicals". Biologicals are defined as substances of biological origin that are used in prophylaxis, therapy or diagnosis of human diseases. In practice this covers vaccines, blood products, biological therapeutics and *in vitro* diagnostics that are important to global public health. This responsibility is discharged via a series of expert meetings that develop and approve these standards through a process of broad consultation and with support from WHO Collaborating Centres.

The committee most relevant to the subject of this consultation is the Expert Committee on Biological Standardization (ECBS). About 10 experts are selected from one or more expert advisory panel to form the committee. The members act as international experts serving the Organization, not under instruction from host institutions or governments. Their work is coordinated through a Secretariat and the committee meets once a year. Certain decisions can be made by the Secretariat between meetings but proposed new WHO standards normally need to be submitted to the annual meeting. It was noted that the deadline for submission of proposed standards or specifications to the ECBS will be the end of July 2005 for the committee meeting in October 2005.

Dr Wood described the biological standards development process. Proposals for new or revised standards are considered by ECBS and/or the Secretariat. Once a need for a standard is agreed, it is developed by a drafting group or scientific working group or WHO International Laboratories. The process includes consultations with, or involvement of, broad geographic and stakeholder input (academia, regulatory authorities, professional bodies, industry). A mature proposal is then considered by ECBS.

These global written standards are technical specifications that define processes and products of assured quality, safety and efficacy. They are intended to be scientific and advisory in nature and are often used as the basis for national legislation. They have a role

in facilitating international harmonization and the exchange of materials across borders. They are living documents revised in response to scientific advances. Examples of written standards in related fields include:

- Blood, Blood Components and Plasma Derivatives: collection, processing and quality control (WHO TRS 840), and
- Guidelines on Transmissible Spongiform Encephalopathies in relation to biological and pharmaceutical products (WHO/BCT/QSD/2003.01).

Dr Wood discussed the possible role of WHO in the development of other types of standards to support tissue and cell banking, e.g. global measurement standards. These are tools for the comparison of results from different laboratories. They support harmonization of international regulations and are recognized by international standard-setting bodies in the trade sector (e.g. WTO, ISO). Examples of existing standards relevant to this field include antibody standards for hepatitis A, B and E, parvo B19 and toxoplasma, antigen standards for HBsAg and HIV p24 and nucleic acid standards for hepatitis A, B, C, for HIV 1 and for parvo B19.

Dr Wood stressed the importance of basing regulations on sound science. In recognition of this principle, WHO supports state-of-the-art specialist scientific and technical research required to enable informed decision making. It provides a globally coordinated mechanism for collaborative investigation, to communicate risk management advice and risk reduction technical specifications. A topical example is the support for research on procedures and methods to exclude emerging infectious diseases, e.g. SARS.

Areas where WHO standards could be developed for tissues and cells would include donor screening; recipient follow up, product safety, product testing (e.g. for adventitious agents or pyrogenicity) AND biocompatibility testing with devices and product characterization. He noted that WHO supports an international standards development group for gene amplification tests (SoGAT) which may be able to contribute positively to the resolution of problems associated with the validation of NAT for blood samples taken from deceased tissue donors.

In discussion, there was clear consensus that any standards or documents developed for tissue and cell transplantation within WHO should build on existing guidance and regulation rather than starting again.

### **Key Points**

- WHO has a well controlled system for the development and approval of global standards in fields related to transplantation (blood, biologicals, pharmaceuticals)
- WHO standards based on state-of-the-art practice and relevant sound research
- Many areas of tissue and cell transplantation globally would benefit from access to WHO standards

## **Cross-cutting Specifications – the Canadian standards**

Dr Paul Dubord described the structure and approach applied in the development of the Canadian standards. A key aim was to have consistent and rational standards applied across the full range of human material from organs to tissues, cells and gametes (CTOs) which would minimize the risk of disease transmission and graft failure. The need to balance safety and quality with availability was a key goal. The complete framework was to include:

- Standards for organs, tissues and cells
- Regulations
- Surveillance
- Compliance and enforcement.

The standards were formulated as a set of general standards applicable to all CTOs with specific additional product standards for each type of material.

The Canadian Standards Association established a Technical Committee to take the standards forward. They ensured an appropriate mix of representatives with a minimum and maximum membership of health care professionals, government/regulatory authorities and those representing general interests. The development process involving drafting, consultation, redrafting and approval was lengthy and the standards were many years in development. There was a strong commitment to the principles of equality and consensus with broad input from stakeholders. A consensus process includes applying the principles of inclusivity, respect for diverse interests and accountability.

The standards are the property of the Canadian Standards Association and can only be changed through their approved process, which includes the reviewing and vetting of any proposed changes by the Technical Committee. The specific standards cross-refer to the general standards, highlighting only where there are particular requirements that do not apply to other human materials. The full set of standards comprise the following:

- General Standards – Cells, Tissues and Organs for Transplantation and Assisted Reproduction (Z900. 1-03)
- Tissues for Assisted Reproduction (Z900.2.1-03)
- Tissues for Transplantation (Z900.2.3-03)
- Perfusable Organs for Transplantation (Z900.2.3-03)
- Lymphohaematopoietic Cells for Transplantation (Z900.2.4-03)
- Ocular Tissues for Transplantation (Z900.2.5-03).

The scope covers safety for potential and actual donors, recipients, personnel and others. It also addresses all aspects of the process from donation to transplantation including donor suitability assessment, retrieval, processing, preservation, packaging, labelling, storage, quarantine, evaluation, recordkeeping, adverse event reporting, distribution, importation or exportation and recall.

Canadian regulations, including strategies for compliance and enforcement and adverse event reporting are now under development. It includes the ability to receive surveillance information in a timely manner, to analyse it and to provide prompt feedback to stakeholders to facilitate risk management.

The compliance/enforcement system will incorporate a registration scheme initially, to which other tools such as licensing and accreditation may be added.

A cost/benefit analysis conducted by Health Canada revealed that the benefits of adherence to standards will outweigh costs significantly. It will cost an estimated 270 million Canadian dollars over 20 years but the benefits are estimated at 1.1 to 1.7 billion dollars over the same period.

The Canadian Medical Standards cover baseline practices. They are intended to be comprehensive, dynamic, transparent and to respond to current scientific knowledge.

Dr Dubord summarized, saying the Canadian system enhances the ability of the regulators to identify problems and strengthens their control of the safety and efficacy of transplantation.

### **Key Points**

- Comprehensive regulation includes the following:
  - the development of standards
  - the incorporation of relevant aspects of those standards into legally binding regulations
  - a system for ensuring compliance and enforcement
  - a system of surveillance
- To achieve harmonization and consistent efficacy across the transplantation field, cross-cutting requirements need to be identified
- The introduction of a comprehensive regulatory system requires investment but in the long run the benefits outweigh the costs

### **Definition and Classification of CTTx**

Dr Deirdre Fehily described work which had been carried out by WHO, in collaboration with the National Transplant Centre (CNT) in Italy, in preparation for this consultation. It was considered that a 'product-based' approach to safety and quality would be the most practical approach to apply in the global context. It was considered logical to begin by attempting to list the current tissues and cells in use and, from that list, to select a shortlist for which global core specifications could be developed. The definition of these products would be crucial to ensure a consistent global understanding of the product names used.

Using a broad classification of anatomical description, currently transplanted tissues and cells were identified in the following categories:

Bone	Cornea
Cartilage	Sclera
Tendon	Gametes
Meniscus	Bone Marrow
Skin	PBSC
Amniotic membrane	Cord Blood
Heart valve	Cultured cells
Blood vessel	

For the purposes of product identification, it was considered essential to describe tissue and cell products in greater detail. Applying a very detailed description to each product type would result in a very long list of product types with very similar safety and quality requirements.

A medium level of detail was proposed to include an anatomical description, principle method of preservation, whether for autologous or allogeneic use and whether or not a sterilization process has been applied.

Applying these criteria a 'long-list' of 76 product types was constructed including:

- 15 major bone and cartilage products
- 18 soft skeletal tissue products
- 16 skin replacement products
- 10 cardiovascular products
- 3 ocular products
- 4 reproductive tissue products
- 6 HPC products
- 4 cell products.

From these, a shortlist was proposed for which WHO product specifications might be constructed. A tissue or cell product was included in the short-list if:

- it was considered essential for basic health care, or
- there was significant international movement of the product, or
- there existed a commercial market for the product.

On this basis, a shortlist of 21 products was proposed including five skeletal tissue products, five skin products, three amniotic membrane products, cardiovascular tissue products, two ocular tissue products and four haematopoietic progenitor cell products.

The long list and shortlist are shown in Appendix 2.

The participants were asked to consider whether this was the correct list of products to focus on in a global perspective, whether they were correctly defined and whether the

development of basic global safety and quality specifications for these products would impact on patient safety.

### **Key Points**

- WHO should concentrate on basic essential tissue and cell products that are used globally and are moved between countries or marketed commercially
- Existing standards and regulations should be consulted to distil out the fundamental safety and quality requirements for these essential products

## **Proposed Method for Global Specifications for Basic Tissues and Cells**

Dr Fehily described some preliminary work on the drafting of product specifications which had been carried out in preparation for the consultation. It was based on some key principles, as follows:

- To build on existing work internationally
- To distil key fundamental or basic safety and quality requirements
- To focus on the tissue/cell product
- To produce clear, user-friendly documents.

The methodology applied involved a review and comparison of existing international guidance/regulation documents and a selection of national regulations/guidance (FDA, Canada, Australia). National documents were selected where no international document superseded it. Thus, for Europe, the Council of Europe guidance and the European Union directives were included and therefore no national European standards were included whereas the US, Canadian and Australian national documents were reviewed.

The aim was to identify cross-cutting core requirements and specific tissue/cell core requirements and to construct some draft product specifications for discussion. The methodology had certain limitations and constraints. For example, it was acknowledged that documents were reviewed out of context, that the field had constantly changing requirements and therefore guidance was often out of date, that a number of documents included in the review were currently in draft and that the comparison may have been imperfect due to human error.

The documents included in the review are listed in Appendix 3.

The review involved a comparison of requirements reviewed in the following categories:

- Consent, data protection and ethics
- Donor medical and behavioural history exclusions
- Donor testing
- Tissue testing/QC.

To stimulate discussion, very preliminary product specifications were drafted for the proposed shortlist. A structure for each specification was proposed, to include the following elements:

- Product name
- Full product description
- Minimal donor acceptance criteria
  - Minimal consent criteria
  - Minimal medical and behavioural history requirements
  - Minimal donor testing requirements
- Minimal tissue clearance criteria
- Sterility criteria

## Session 6: Core Specifications for Essential CTTx

Participants worked in tissue/cell-specific groups to consider the drafted product specifications relevant to each tissue/cell area. The groups were structured as follows:

1. Musculo-skeletal tissues
2. Skin, amniotic membrane and heart valve tissues
3. Cornea and amniotic membrane tissues
4. Haematopoietic stem cells

The groups fed back to a plenary session. They expressed a general consensus regarding the usefulness of a set of WHO product specifications; the need for WHO to actively promote the local adoption of the specifications was stressed. It was agreed that the specifications should be combined in a single document with a preamble. The latter should include the importance of risk/benefit rationale in the acceptance or rejection of a tissue or cell donation for transplantation. A glossary of terms and definitions should be included in the document. The preamble should explain that general issues relating to the requirements for quality management/Good Tissue Practice, etc. would be detailed via a WHO Aide Mémoire.

There were various suggestions to consolidate some product specifications and to add others but overall the result will be to reduce the shortlist considerably. Some suggested that the generic (cross-cutting) requirements should be included in one document and the tissue/cell-specific requirements be separate. It was suggested that the issue of the validity of serological or NAT tests on donors should be highlighted. It was proposed that a requirement for serum archives should be removed as this is not a requirement in a number of countries. The issue of consent in living donors who are minors was one which was highlighted as needing addressing.

Many participants suggested that product descriptions could be simplified by, for example, addressing sterility within a technical specification. The need to address the use of normally ineligible products was also highlighted though this might be addressed in the preamble. It was acknowledged that the medical director needed to have discretion for specific exclusionary criteria, dependent on the specific patient's needs and clinical circumstances. Many other specific comments were documented for collation and consideration when the specifications are redrafted.

The resulting draft core specifications are available on request to WHO/HTP/EHT/CPR and will be published on the WHO website.

### Key Points

- Cross-cutting requirements should be identified to achieve harmonization across the field
- Product specifications should address donor selection, testing, contamination control, packaging and labelling
- Quality system requirements should be addressed in a separate document

## **Session 7: Access and international circulation of CTTx**

### **Haematopoietic Stem Cells**

Dr. Dennis L. Confer, Chief Medical Officer, National Marrow Donor Program (NMDP), USA, spoke on behalf of the World Marrow Donor Association (WMDA) on access and the international circulation of haematopoietic stem cells (HSC) from peripheral and umbilical cord blood. He described an active worldwide exchange of cells for transplantation that is built on a number of systems that provide access for patients to life-saving therapy and facilitate international exchange. These systems also protect donors and, more importantly, collect a variety of data on the donor registries, transplant activities, patient outcomes and, more recently but developing quickly, adverse events. These systems also allow the tracking of products from their origin to destination and trace them back again.

Dr Confer attributed much of the progress in this area to two critical organizations. These are the WMDA, a collaboration of adult donor and cord blood registries founded in 1994, and the Bone Marrow Donors Worldwide (BMDW) organization, established in the late 1980s, that provides an Internet-based listing of 91 registries from 40 nations. WMDA facilitated 6,385 transplants in 2003 where fully one third of the products crossed a border into another country for transplantation. Transplant activity was greatest in the US, Germany, Japan, the UK and France.

He attributed the well developed systems for international exchange for these CTTx to the need for a HLA match for successful transplant outcomes. Most people who need a transplant do not have a matched family donor and must turn to unrelated adult donors or cord blood units. Data was presented showing that finding a good match in one's own country is related to the size and HLA diversity represented in the country's registry. For example, the NMDP with 100,000 identified donors provides matches for just over 40% of the US patient population, whereas a Japanese registry of 100,000 donors can provide 85% of the matches for their patients with more homogenous HLA types.

Dr Confer then described the activities of two of the largest repositories of patient outcome data. These are the European Blood and Marrow Transplant Group (EBMT), which collects data from more than 500 centres in 60 countries, and the Center for International Blood and Marrow Transplant (CIBMTR) in the US, which collects data from more than 450 centres in 48 countries. He indicated that there is some overlap in reporting to these groups. These data evaluate mortality after unrelated donor transplantation for a variety of indications.

He emphasized that there is a need to facilitate the development of new registries and entry into the worldwide systems he described. This can be accomplished with meetings to share information such as the 5<sup>th</sup> International Donor Registry Conference held last May in Tokyo where reports from many established and emerging Asian registries were discussed. Areas of concern identified at that conference include funding to grow their registries and serve their patient populations, the need for accreditation and global standards, the need to access the WMDA and its support systems, the need to acquire information system management and the desire for continued collaboration. The European Marrow Donor Information System (EMDIS) and the A Growable Network Information System (AGNIS) that is being developed in the US are examples of successful information systems that provide

automated exchange of donor search information. Dr Confer indicated that these should serve as models for the international exchange of transplant information to both locate donors and to evaluate outcomes. He concluded by emphasizing the value of facilitating international collaboration, protecting donors and providing patient access to these life-saving therapies. He highly recommended WHO support for the extension of these established systems rather than for developing new ones.

## **Corneas**

Dr Upali Mendis from the Eye and Tissue Bank of Sri Lanka described their experience and procedures for the banking of corneas. The process begins with the assessment of donor suitability. This is based on consent of the family, age and the risk of transmission. Donations are not accepted where there is a risk of rabies, Creutzfeldt-Jakob disease, viral hepatitis, death due to septicaemia or any history of intraocular surgery. There are also exclusions applied where the potential donor has had an intrinsic eye disease. Testing is performed for HIV, hepatitis B and C and syphilis. Following retrieval, corneas are examined under the slit lamp microscope for any pathology. Whole eyes are stored in a sterile moist chamber (glass bottle) at 4°C. Corneal buttons with corneoscleral rims are stored in M-K medium, MEM or optisol medium, at 4°C.

The Eye Bank maintains a record of all donations including:

- Informed consent
- Donor's name, age, cause of death, date and time of death
- Date and time of enucleation
- Particulars about the recipient.

Whole eyes or corneal buttons are transported in rigid foam boxes packed with ice and labelled with the name of tissue, name and address of Eye Bank, donor identification number, age of donor, date, time and cause of death. All establishments receiving corneas maintain records of all recipient and donor information. Transplantation ophthalmologists must maintain a record of the condition of the donor material at the time of receipt and inform the Eye Bank of the outcome of transplant surgery. If the recipient develops a transmissible disease attributed to the transplantation, the Eye Bank and the public health authorities are informed in writing without delay.

## **Heart Valves**

Dr Arlinke Bokhorst of the BIS Foundation in The Netherlands provided an overview of the international circulation of human cardiovascular tissues for transplantation. Since 1960 donated material has been used for the replacement of diseased, degenerated or congenitally anomalous aortic valves, pulmonary valves, occasional mitral valves and blood vessels. There are various options for the replacement of a heart valve. In 40% of cases, a mechanical valve is used and in 45% of cases a pig valve. Allografts and autografts have specific advantages in particular clinical circumstances. Patients who should be treated with a homograft include women who are fertile, patients with acute endocarditis or aortic root disease, patients whose requirement is for a valve of <22 mm diameter and children or young adults who still have growth potential.

Data on demand and supply through BIS suggests that there are shortages of particular sizes of aortic valves and generally of pulmonary valves of all sizes. BIS facilitates considerable exchanging of heart valves between the countries of Europe. There is also considerable global export of heart valves, mainly from the US and Europe to the rest of the world. There are heart valve banks in most developed countries but almost none in most parts of Africa and large parts of South America and Asia.

The areas of the world that have the highest incidence of death from rheumatic heart disease (China, India, Pakistan, South Central Asia and the Russian Federation) are also the areas that are least well supplied with banks. In 2003 it is estimated that over one million children between the ages of five and 14 died of rheumatic heart disease in Sub-Saharan Africa. Almost three quarters of a million died from this condition in South-Central Asia.

The overall picture, therefore, is one of relative shortage of heart valves for transplantation in developed countries and an absolute shortage in many developing countries. In many areas there are no active donor programmes and no infrastructure to facilitate the development of these services. Homograft valve transplants mean that the patients do not require anticoagulant therapy so there are considerable cost savings. There are also fewer complications and fewer re-operations where human valves are used and they tend to be cheaper than mechanical or pig valves.

It is essential that minimum standards of safety and quality of valves are assured for exported tissues. There needs to be support for the development of national programmes in many countries. There should be links between established banks and newly developing ones to allow the transfer of knowledge, information, training, etc. It is also essential that training is provided for surgeons to ensure the success of human valve transplantation.

### **Distribution of Tissues by US Banks to Other Countries**

Mr Scott Brubaker, Chief Policy Officer, American Association of Tissue Banks (AATB), provided some additional pertinent information on the international distribution of tissues derived from a 2002 survey of 59 accredited tissue banks. Twenty-eight of these banks indicated that they distribute tissues outside the United States to 39 countries. Tissues distributed included a variety of musculo-skeletal products, skin and amniotic membrane.

Most of the countries to which tissue was shipped are represented at this meeting. Overall distribution (within or outside the US) by the 41 banks who responded to the survey approximated the following allograft activity: 906,000 MS; 52,000 soft tissues; 2,015 heart valves; 900 vascular and 12,000 sq. ft. of skin. There were only two confirmed reports of bacterial/fungal infections in recipients and no fatal complications.

**Key Points**

- There is considerable experience in the global sharing of tissues and cells, particularly haematopoietic stem cells, corneas and heart valves
- National health authorities need to implement regulatory systems which control importation to ensure quality and safety
- Regulations must be stringent must also facilitate access to essential CTTX not available locally
- Collaboration between clinicians and national regulatory authorities allows access to vital HLA compatible HSC products, even in circumstances of exceptional product release. The development of regulation globally must not have a detrimental affect on this activity

## Session 8: Next Steps

### **Cells and Tissues for Transplantation: From Basic to Biotech – The Australian Regulatory Approach**

Dr Albert Farrugia described the role of Australia's Therapeutic Goods Administration (TGA), which is a division of the Department of Health and Ageing. The TGA regulates the safety, quality and efficacy of therapeutic goods available in Australia and primarily operates under cost recovery arrangements. The main experience of the TGA is in pharmaceutical regulation. Emerging biological therapies have mostly been exempt from the regulatory authority of the TGA and therefore there is limited experience and difficulty in regulating therapeutic procedures that are closely aligned with medical practice or part of the public health.

Dr Farrugia described some of the differences between mainstream pharmaceutical and cell and tissue products that result in regulatory challenges. Mainstream pharmaceuticals involve large production batches, high throughput, open systems, control of starting material, complex processes, a high degree of development and stability, unknown recipients and short expiry and storage dates. In contrast, cell and tissue products involve single products, low throughput, closed systems, labour-intensive processes, limited control of starting materials, research-based protocols that are constantly evolving, varying processes and often long expiry and storage dates. Some additional issues of concern with viable cell and tissue products include the elimination of pathogens and the challenge of terminal sterilization or filtration, the critical nature of storage conditions and the often urgent clinical need for the product.

Dr Farrugia reviewed some of the reasons why the regulation of cell and tissue therapies is necessary. Cells and tissues have transmitted disease, including bacterial infections, to recipients and the prevalence of viral markers in tissue donors is higher than in first time blood donors. Unsubstantiated and exaggerated claims have been made for some products. Regulation can improve the quality of outcomes for patients.

Dr Farrugia explained the development of the TGA's regulatory framework for cells and tissues. In 2002 the Australian Health Minister's Conference tasked the TGA with developing a new framework for cells and tissues by the highest level of government. A significant challenge involved determining the scope of the initiative. In Australia medicines and devices are clearly defined. Tissues and cellular therapies may fall within the definition of medicines or within the definition of devices, or may fall outside the scope of current TGA authority. A primary assumption of the TGA's regulatory framework for cell and tissue therapies is that the intensity of processing and the level of manipulation directly impact the risk profile and that these characteristics should therefore be the basis for the level of regulation.

The TGA proposes defining human cell and tissue therapies (HCT/Ps) to include all articles containing or consisting of, or derived from, human cells or tissues that are intended for implantation, transplantation, infusion or transfer into a human recipient. The proposed framework includes three levels of regulation. Class 3 includes a combination of an HCT/P with a non-tissue part, an HCT/P with pharmacological, chemical or metabolic effect in the patient, an HCT/P where usage is different from the original physiological source ("non-

homologous" use), an HCT/P that is manipulated so that relevant biological or structural function is altered and an HCT/P made using cell expansion cell-based gene therapy or similar techniques. Class 2 HCT/Ps are those that do not fall into Class 3 and are banked. Class 1 HCT/Ps are those that do not fall into Classes 2 or 3 (for example, organs for transplantation).

Class 1 HCT/Ps would be required to comply with standards of good tissue practice. For some tissues and organs current industry standards may be adopted. Class 2 HCT/Ps would be required to comply with relevant current good manufacturing practice, which would include good tissue practice, and licensing of the manufacturer would be required. Class 3 HCT/Ps would follow Class 2 requirements and would in addition be subject to quality, safety and efficacy assessment and registry requirements. The current proposal would exempt surgical procedures from regulation.

The proposed regulatory scheme will be overseen through a new regulator operating under a new part of the relevant legislation. The intention is to move from a prescriptive framework to a more flexible one, allowing entry of new technologies as they mature. The level of regulation will be linked to the risk/benefit ratio as determined by the classification of the therapy. The TGA continues to engage on the proposed classification and the risk/benefit principles to be applied.

#### **Key Points**

Regulation can improve the quality of outcomes for patients.

- Risk:benefit ratio should determine the classification of the therapy and consequently the level of regulation applied
- Prescriptive regulatory frameworks need to become more flexible to enable new technologies to be effectively incorporated, as they emerge

## **Future Work and Conclusions**

Dr Noël thanked all the participants for their input in a very dense meeting. This first global consultation on regulatory requirements for CTTx demonstrated the need and importance of global cooperation. During this meeting the seed has been planted of an international network of stakeholders to work not only at ensuring global safety, quality and efficacy of CTTx but also at promoting access to suitable transplantation. Countries that have not yet developed the oversight of CTTx should benefit from the experience of those who are more advanced.

From the contribution to the meeting a report with key points will be forwarded to all participants for their validation. Likewise the draft core specifications will be modified according to the requests expressed during the meeting, always keeping to the rule of identifying the essential requirements and seeking simplicity. These documents will be circulated to all participants for their approval or further suggestions. They will be further circulated to experts and representatives of national regulatory authorities and ultimately proposed to the Expert Committee on Biological Standardization. Key points collected during the meeting will provide the basis for a first draft of an Aide Mémoire on human cells and tissues for transplantation which will also be circulated to participants.

Sharing information at the global level is essential to the process of moving towards harmonization. Access and safety issues involve the global community as CTTx circulate cross boundaries. It is also crucial to share experiences of types of threat. It is expected that future work in the area of CTTx will continue along the lines drawn during this meeting and concentrate on increasing visibility at national, regional and global levels of activity in human cell and tissue procurement, processing, banking and transplantation, as well as creating a global system of reference for essential requirements.

# APPENDIX 1

## World Health Assembly Resolution WHA57.18 (May 2004)

### Human organ and tissue transplantation

The Fifty-seventh World Health Assembly,

Recalling resolutions WHA40.13, WHA42.5 and WHA44.25 on organ procurement and transplantation;

Having considered the report on human organ and tissue transplantation;

Noting the global increase in allogeneic transplantation of cells, tissues and organs;

Concerned by the growing insufficiency of available human material for transplantation to meet patient needs;

Aware of ethical and safety risks arising in the transplantation of allogeneic cells, tissues and organs, and the need for special attention to the risks of organ trafficking;

Recognizing that living xenogeneic cells, tissues or organs, and human bodily fluids, cells, tissues or organs that have had *ex vivo* contact with these living xenogeneic materials, have the potential to be used in human beings when suitable human material is not available;

Mindful of the risk associated with xenogeneic transplantation of the transmission of known or as yet unrecognized xenogeneic infectious agents from animals to human beings and from recipients of xenogeneic transplants to their contacts and the public at large;

Recognizing that transplantation encompasses not only medical but also legal and ethical aspects, and involves economic and psychological issues,

### Allogeneic transplantation

1. URGES Member States:

(1) to implement effective national oversight of procurement, processing and transplantation of human cells, tissues and organs, including ensuring accountability for human material for transplantation and its traceability;

(2) to cooperate in the formulation of recommendations and guidelines to harmonize global practices in the procurement, processing and transplantation of human cells, tissues and organs, including development of minimum criteria for suitability of donors of tissues and cells;

(3) to consider setting up ethics commissions to ensure the ethics of cell, tissue and organ transplantation;

(4) to extend the use of living kidney donations when possible, in addition to donations from deceased donors;

(5) to take measures to protect the poorest and vulnerable groups from “transplant tourism” and the sale of tissues and organs, including attention to the wider problem of international trafficking in human tissues and organs;

## 2. REQUESTS the Director-General:

(1) to continue examining and collecting global data on the practices, safety, quality, efficacy and epidemiology of allogeneic transplantation and on ethical issues, including living donation, in order to update the Guiding Principles on Human Organ Transplantation;<sup>1</sup>

(2) to promote international cooperation so as to increase the access of citizens to these therapeutic procedures;

(3) to provide, in response to requests from Member States, technical support for developing suitable transplantation of cells, tissues or organs, in particular by facilitating international cooperation;

(4) to provide support for Member States in their endeavours to prevent organ trafficking, including drawing up guidelines to protect the poorest and most vulnerable groups from being victims of organ trafficking;

<sup>1</sup> Document WHA44/1991/REC/1, Annex 6.

## II

### **Xenogeneic transplantation**

#### 1. URGES Member States:

(1) to allow xenogeneic transplantation only when effective national regulatory control and surveillance mechanisms overseen by national health authorities are in place;

(2) to cooperate in the formulation of recommendations and guidelines to harmonize global practices, including protective measures in accordance with internationally accepted scientific standards to prevent the risk of potential secondary transmission of any xenogeneic infectious agent that could have infected recipients of xenogeneic transplants or contacts of recipients, and especially across national borders;

(3) to support international collaboration and coordination for the prevention and surveillance of infections resulting from xenogeneic transplantation;

#### 2. REQUESTS the Director-General:

(1) to facilitate communication and international collaboration among health authorities in Member States on issues relating to xenogeneic transplantation;

(2) to collect data globally for the evaluation of practices in xenogeneic transplantation;

(3) to inform proactively Member States of infectious events of xenogeneic origin arising from xenogeneic transplantation;

(4) to provide, in response to requests from Member States, technical support in strengthening capacity and expertise in the field of xenogeneic transplantation, including policy-making and oversight by national regulatory authorities;

(5) to report at an appropriate time to the Health Assembly, through the Executive Board, on implementation of this resolution.

Eighth plenary meeting, 22 May 2004  
A57/VR/8

## APPENDIX 2

### WHO Draft Tissue and Cell Product List

#### List of cell and tissue products

<b>Tissue Description – Bone and Cartilage Products</b>	<b>Rationale for Inclusion in/Exclusion from Shortlist</b>
Unprocessed frozen bone	Basic tissue product, banked and used worldwide
Sterilized unprocessed frozen bone	Many developing countries use irradiation to sterilize bone which has otherwise not been processed
Aseptically washed (marrow depleted) frozen bone	Aseptic processing not common in developing countries No (or very small) international market
Sterilized, washed (marrow depleted) frozen bone	Marrow depletion not common in developing countries No (or very small) international market
Lyophilised bone (aseptically processed)	Significant/large international market
Sterilized, lyophilised bone	Significant/large international market
Bone with cryopreserved articular cartilage	Low volume activity No (or very small) international market
Demineralised, lyophilised bone (aseptically processed)	Although international market exists, product used in private dental procedures and very little in developing countries Carries very low infective risk
Sterilized, demineralised lyophilised bone	Although international market exists, product used in private dental procedures and very little in developing countries Carries very low infective risk
Unprocessed frozen cartilage	Low volume activity No (or very small) international market

Aseptically washed, frozen cartilage	Low volume activity No (or very small) international market
Sterilized, washed frozen cartilage	Low volume activity No (or very small) international market
Lyophilised cartilage (aseptically processed)	Low volume activity No (or very small) international market
Sterilized, lyophilised cartilage	Low volume activity No (or very small) international market
Cryopreserved cartilage	Low volume activity No (or very small) international market

<b>Tissue Description – Soft Skeletal Tissue Products</b>	<b>Rationale for Inclusion in/Exclusion from Shortlist</b>
Unprocessed frozen tendon	Basic tissue product, banked and used worldwide
Aseptically washed, frozen tendon	Aseptic processing not common in developing countries No (or very small) international market
Aseptically washed, cryopreserved tendon	Aseptic processing not common in developing countries No (or very small) international market
Sterilized, washed frozen tendon	Low volume activity No (or very small) international market
Lyophilised tendon (aseptically processed)	Aseptic processing not common in developing countries No (or very small) international market
Sterilized lyophilised tendon	Low volume activity No (or very small) international market
Unprocessed frozen fascia lata	Low volume activity No (or very small) international market
Aseptically washed, frozen fascia lata	Aseptic processing not common in developing countries No (or very small) international market
Aseptically washed, cryopreserved fascia lata	Aseptic processing not common in developing countries No (or very small) international market
Sterilized, washed frozen fascia lata	Low volume activity No (or very small) international market
Lyophilised fascia lata (aseptically processed)	Aseptic processing not common in developing countries

	No (or very small) international market
Sterilized lyophilised fascia lata	Low volume activity No (or very small) international market
Unprocessed frozen meniscus	Low volume activity No (or very small) international market
Aseptically washed, frozen meniscus	Aseptic processing not common in developing countries No (or very small) international market
Aseptically washed, cryopreserved meniscus	Aseptic processing not common in developing countries No (or very small) international market
Sterilized, washed frozen meniscus	Low volume activity No (or very small) international market
Lyophilised meniscus (aseptically processed)	Aseptic processing not common in developing countries No (or very small) international market
Sterilized lyophilised meniscus	Low volume activity No (or very small) international market

<b>Tissue Description – Skin Replacement Products</b>	<b>Product Characteristics not Included in Description</b>
Fresh unprocessed skin	Basic tissue product, banked and used worldwide
Cryopreserved skin	Basic tissue product, banked and used worldwide
Glycerolised skin	Basic tissue product, banked and used worldwide International market exists
Sterilized glycerolised skin	Low volume activity No (or very small) international market
Air dried/Lyophilised skin	Basic tissue product, banked and used in many developing countries
Sterilized air-dried/lyophilised skin	Basic tissue product, banked and used in many developing countries
Autologous cultured epidermis	Low volume activity No (or very small) international market
De-epidermized dermis	Low volume activity No (or very small) international market
Sterilized de-epidermized dermis	Low volume activity No (or very small) international market
Skin composite	Low volume activity International market in developed countries only
Fresh unprocessed amniotic membrane	Basic tissue product, banked and used in many developing countries
Cryopreserved amniotic membrane	Low volume activity No (or very small) international market
Glycerolised amniotic membrane	Low volume activity No (or very small) international market
Air dried/lyophilised amniotic membrane	Basic tissue product, banked and used in many developing countries

Sterilized glycerolised amniotic membrane	Low volume activity No (or very small) international market
Sterilized air-dried/lyophilised amniotic membrane	Many developing countries use irradiation to sterilize dried amniotic membrane

<b>Tissue Description – Cardiovascular Tissue Products</b>	<b>Rationale for Inclusion in/Exclusion from Shortlist</b>
Fresh unprocessed aortic valve	Low volume activity No (or very small) international market
Cryopreserved aortic valve	Basic tissue product, banked and used worldwide International market exists
Fresh unprocessed pulmonary valve	Low volume activity No (or very small) international market
Cryopreserved pulmonary valve	Basic tissue product, banked and used worldwide International market exists
Fresh unprocessed mitral valve	Low volume activity No (or very small) international market
Cryopreserved mitral valve	Low volume activity No (or very small) international market
Fresh unprocessed artery	Low volume activity No (or very small) international market
Cryopreserved artery	Low volume activity No (or very small) international market
Fresh unprocessed vein	Low volume activity No (or very small) international market
Cryopreserved vein	Low volume activity

	No (or very small) international market
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<b>Tissue Description – Ocular Products</b>	<b>Rationale for Inclusion in/Exclusion from Shortlist</b>
Fresh unprocessed cornea	Basic tissue product, banked and used worldwide International market exists
Cornea stored in culture medium	Basic tissue product, banked and used worldwide International market exists
Non-viable sclera	Low volume activity No (or very small) international market

<b>Tissue Description – Reproductive Tissues and Cells</b>	<b>Rationale for Inclusion in/Exclusion from Shortlist</b>
Cryopreserved ovarian tissue	Low volume activity No (or very small) international market
Cryopreserved testicular tissue	Low volume activity No (or very small) international market
Cryopreserved gametes	High volume activity but no international market
Cryopreserved embryos	Low volume activity No (or very small) international market

<b>Cell Description – Haematopoietic Progenitor Cells</b>	<b>Rationale for Inclusion in/Exclusion from Shortlist</b>
Fresh bone marrow (allogeneic, unrelated)	Significant international market exists
Cryopreserved bone marrow (autologous)	Low volume activity

	No (or very small) international market
Fresh peripheral blood stem cells (allogeneic, unrelated)	Significant international market exists
Cryopreserved peripheral blood stem cells (autologous)	Low volume activity No (or very small) international market
Cryopreserved cord blood (allogeneic, unrelated)	Significant international market exists
Cryopreserved cord blood (autologous or directed)	Developing international market (private companies direct to patients)

<b>Cell Description – Other Cells</b>	<b>Rationale for Inclusion in/Exclusion from Shortlist</b>
Fresh pancreatic islet cells	Low volume activity No (or very small) international market
Cultured chondrocytes (autologous)	Low volume activity No (or very small) international market
Cultured limbal cells (autologous)	Low volume activity No (or very small) international market
Cultured epidermal cells (autologous)	Low volume activity No (or very small) international market

### **Proposed Shortlist of Products**

Unprocessed frozen bone  
 Specification will be sterilized unprocessed frozen bone  
 Lyophilised bone (aseptically processed)  
 Sterilized, lyophilised bone  
 Unprocessed frozen tendon  
 Fresh unprocessed skin  
 Cryopreserved skin  
 Glycerolised skin

Air-dried/lyophilised skin  
Sterilized air-dried/lyophilised skin  
Fresh unprocessed amniotic membrane  
Air dried or lyophilised amniotic membrane  
Sterilized air-dried/lyophilised amniotic membrane  
Cryopreserved aortic valve  
Cryopreserved pulmonary valve  
Fresh unprocessed cornea  
Cornea stored in culture medium  
Fresh bone marrow (allogeneic, unrelated)  
Fresh peripheral blood stem cells (allogeneic, unrelated)  
Cryopreserved cord blood (allogeneic, unrelated)  
Cryopreserved cord blood (autologous or directed)

### Documents included in the review

#### **Council of Europe**

Guide to Safety and Quality Assurance for Organs, Tissue and Cells. Second Edition, September 2004. (Can be purchased at: [http://book.coe.int/EN/ficheouvrage.php?PAGEID=36&lang=EN&produit\\_aliasid=1794](http://book.coe.int/EN/ficheouvrage.php?PAGEID=36&lang=EN&produit_aliasid=1794))

#### **European Union**

Directive 2004/23/EC (entered into force 7<sup>th</sup> April 2004. (Deadline for transposition into national law by EU Member States 7 April 2006: [http://europa.eu.int/eur-lex/pri/en/oj/dat/2004/l\\_102/l\\_10220040407en00480058.pdf](http://europa.eu.int/eur-lex/pri/en/oj/dat/2004/l_102/l_10220040407en00480058.pdf) ) Technical Requirements associated with the above Directive – under development during 2004/05 by EU comitology procedure:

Commission Directive 1: Technical requirements for the donation, procurement and testing of human tissues and cells. (Draft issued for consultation, August 2004: [http://europa.eu.int/comm/health/ph\\_threats/human\\_substance/oc\\_tech\\_cell/oc\\_tech\\_cell\\_draft\\_en.pdf](http://europa.eu.int/comm/health/ph_threats/human_substance/oc_tech_cell/oc_tech_cell_draft_en.pdf))

#### **UN**

International Atomic Energy Agency Standards for Tissue Banking: ([www.int-tissuebank.com](http://www.int-tissuebank.com)).

#### **FDA**

Eligibility Determination for Donors of Human Cells, Tissues and Cellular and Tissue-based Products; Final Rule, May 2004 (21 CFR parts 210, 211, 820 and 1271. Federal Register Vol. 69, number 101: [www.fda.gov/cber/rules/suitdonor.pdf](http://www.fda.gov/cber/rules/suitdonor.pdf))

Draft Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-based Products, May 2004 ([www.fda.gov/cber/gdlns/tissdonor.pdf](http://www.fda.gov/cber/gdlns/tissdonor.pdf))

Draft Guidance for Industry: Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jacob disease (CJD) and Variant Creutzfeldt-Jacob disease (vCJD) by human cells, tissues and cellular and tissue based products, June 2002. ([www.fda.gov/cber/gdlns/cjdvcjd0602.pdf](http://www.fda.gov/cber/gdlns/cjdvcjd0602.pdf))

Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement: Proposed Rule. January 2001. ([www.fda.gov/cber/rules/gtp.pdf](http://www.fda.gov/cber/rules/gtp.pdf))

#### **Australian Therapeutic Goods Administration (TGA)**

Code of Good Manufacturing Practice – Human Blood and Tissues, August 2000. ([www.tga.gov.au/docs/pdf/gmpbltic.pdf](http://www.tga.gov.au/docs/pdf/gmpbltic.pdf))

## **Canadian Standards Association Z900 standards**

Cells, Tissues, and Organs for Transplantation and Assisted Reproduction: General Requirements (Z900. 1-03)

Tissues for Transplantation (Z900.2.2)

Lymphohematopoietic Cells for Transplantation (Z900.2.5 – 03)

Ocular Tissues for Transplantation (Z900.2.4 – 03)

(Can be purchased at: [http://www.csa-intl.org/onlinestore/ISO\\_Search\\_Results.asp?query=Z900&x=15&y=8](http://www.csa-intl.org/onlinestore/ISO_Search_Results.asp?query=Z900&x=15&y=8) )

## **Joint Accreditation Committee of ISCT and EBMT (JACIE)**

Standards for Haematopoietic Progenitor Cell Collection, Processing and Transplantation

2nd Edition

([www.ebmt.org/8TransplantGuidelines/guideline\\_docs/English/JACIE\\_second\\_edition\\_june2003.pdf](http://www.ebmt.org/8TransplantGuidelines/guideline_docs/English/JACIE_second_edition_june2003.pdf))

## **JACIE/FAHCT/NetCord**

Standards for cord blood banking and transplantation. (Can be purchased at [http://www.unmc.edu/Community/fahct/Interactive\\_Pub\\_CORDBlood\\_orderform.pdf](http://www.unmc.edu/Community/fahct/Interactive_Pub_CORDBlood_orderform.pdf) )

## **European Association of Tissue Banks (EATB)**

Tissue Bank Standards Draft revision 2004. (Pre-revision version can be ordered at <http://www.eatb.de/html/standards.htm> )

## **American Association of Tissue Banks (AATB)**

Tissue Bank Standards. (Can be ordered at: [www.aatb.org](http://www.aatb.org))

## **European Eye Bank Association (EEBA)**

Minimum Standards – draft revision September 2004. (Previous version, September 2000 available at: [http://www.eeba.net/agreements\\_on\\_minimum\\_standards.htm](http://www.eeba.net/agreements_on_minimum_standards.htm) )

## **Eye Bank Association of America (EBAA)**

Medical Standards. (Can be ordered at: <http://www.restoreight.org/general/medstndprocedureman.pdf>)

## **Health Canada**

Directive and Guidance Document.

([http://www.hc-sc.gc.ca/hpfb-dgpsa/bgtd-dpbtg/cto\\_directive\\_e.html](http://www.hc-sc.gc.ca/hpfb-dgpsa/bgtd-dpbtg/cto_directive_e.html) )

## APPENDIX 4

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**Global consultation on regulatory requirements  
for human cells and tissues for transplantation (CTTx)**

**29 November – 1 December 2004, Ottawa, Canada**

**Programme of Work**

**Monday 29 November 2004**

**08:30-09:45 Opening session**

Welcome of participants

Opening addresses:

- Health Canada
- Public Health Agency of Canada
- WHO

TBA

Vladimir Lepakhin

Introduction of participants

Comments on Agenda

Election of Chairperson and Rapporteurs

**09:45-10:30 Session 1: Introduction**

- WHO and transplantation, World Health Assembly Resolution WHA 57.18 Luc Noël
- Objectives and expected outcomes for the consultation Luc Noël
- Cell and Tissue Regulatory oversight, example of Canada in a global perspective TBA

**10:30-10:45 Coffee/Tea break**

**10:45-13:00 Session 2: Global issues in CTTx**

- 10:45-11:10 Tunisia, Iran, Pakistan
- 11:10-11:35 India, Sri Lanka, Thailand
- 11:35-12:05 Australia, China, Japan, Korea
- 12:05-13:00 Argentina, Brazil, Colombia, Cuba, Association of Latin American Tissue Banks (ALATB), Eye Bank Association of America (EAAB), American Association of Tissue Banks (AATB) USA, Canada

**13:00-14:00 Lunch break**

**14:00-15:45 Session 2: Global issues in CTTx (continued)**

- 14:00-14:15 Nigeria, South Africa
- 14:15-14:25 Council of Europe
- 14:25-14:35 European Union

- 14:35-15:15 France, Germany, Italy, United Kingdom, The Netherlands, Slovakia,  
Russia, European Association of Tissue Banks (EATB)
- 15:15-15:35 Regulatory oversight and surveillance of cells and tissues for  
transplantation, experience of the USA Jill Hartzler Warner

**15:40-16:00** *Coffee break*

**16:00-16:30** **Session 2: Global issues in CTTx (continued)**

- 16:00-16:30 General discussion: global issues in CTTx

**16:30-18:00** **Session 3: Safety and Surveillance in CTTx**

- 16:30-16:50 The global need for risk assessment and essential requirements for cells and  
tissues Tony Giulivi
- 16:50-17:10 Towards a Global Knowledge Database on risks and safety measures for  
infections associated to human material for therapeutic use Silvano Wendel
- 17:10-18:00 General discussion: safety and surveillance in CTTx, global  
implications
- 18:00-18:15 Summary of the day Rapporteurs/Secretariat

**18:15** *End of Day 1*

Tuesday 30 November 2004

**08:00-10:30** **Session 4: CTTx: Essentials for good practice, governance  
and oversight**

- 08:00-08:20 The role of national health authorities in ensuring access to safe  
effective and quality CTTx Bernard Loty
- 08:20-08:40 Essential process requirements for cell and tissue transplantation  
from procurement to follow-up of recipients Yeowon Sohn
- 08:40-10:00 General discussion: essentials for good practice, governance and  
oversight
- 10:00-10:30 Recapitulation and element for an aide-mémoire for CTTx Rapporteurs/  
Secretariat

**10:30-10:45** *Coffee/Tea break*

**10:45 -13:00** **Session 5: Cross-cutting specifications for CTTx**

- 10:45-10:55 Normative work at WHO David Wood
- 10:55-11:15 Definition and classification of CTTx Deirdre Fehily
- 11:15-11:35 Cross-cutting specifications for CTTx, the example of the  
Canadian standards Paul Dubord
- 11:35-11:50 Proposed method for global core specifications for cells and  
tissues for transplantation Deirdre Fehily
- 11:50-13:00 General discussion: common requirement for CT for transplantation

**13:10-14:00** *Lunch break*

## **14:00 -15:45 Session 6: Core specifications for essential CTTx**

14:00-15:30 Breakout groups: core specifications:

- bone musculo-skeletal George Galea/Bernard Loty
- skin heart valves Ján Koller/Deirdre Fehily
- cornea amniotic membrane Naoshi Shinozaki/Virender Singh Sangwan
- haematopoietic stem cells Yeowon Sohn/Denis Confer

**15:40-16:00 Coffe/Tea break**

## **16:00-17:45 Session 6: Core specifications for essential CTTx (continued)**

16:00-17:45 Report and discussions

17:45:18:00 Summary of the day

Rapporteurs/Secretariat

**18:00 End of Day 2**

Wednesday 1 December 2004

## **08:00-10:30 Session 7: Access and international circulation of CTTx**

08:00-08:20 Haematopoietic stem cells

Denis Confer

08:20-08:40 Cornea

Upali Mendis

08:40-09:00 Heart valves

Arlinke Borkhorst

08:40-10:30 General discussion: international circulation of CTTx

**10:30-10:45 Coffee/Tea break**

## **10:30-12:30 Session 8: Next steps**

10:45-11:05 Cells and tissues for transplantation from basic to biotech.

Albert Farrugia

11:05-12:00 General discussion: future work and planning

12:00-12:30 Adoption of recommendations, planning for future work and  
conclusions

Rapporteurs/Secretariat

12:30-13:00 Session 9: Closing session

**13:00 End of meeting**

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