World Health Organization

AIDE-MÉMOIRE ON KEY SAFETY REQUIREMENTS FOR ESSENTIAL MINIMALLY PROCESSED HUMAN CELLS AND TISSUES FOR TRANSPLANTATION

Introduction

This document on tissue and cell transplantation to improve patient care, is the first in a series aiming to assist regulators, tissue bank operators and clinical users of tissue and cell transplant globally by providing guidance on safety and quality requirements for the most used and distributed human tissues and cells. The present document provides 'product' based safety requirements. They are designed to define international expectations for essential testing, donor selection and processing of human cells and tissues for transplantation (HCTT). These safety requirements have been developed by reference to existing standards and regulations in the field. They also provide guidance on the content of the information to be provided with the product either on the label or in the accompanying documentation.

It was deemed a priority to provide guidance on quality and safety for human cell and tissue products for transplantation that would define core criteria for products acceptable to meet patient needs. Nevertheless it should be emphasized that human cell and tissue products for transplantation result from a process spanning from donor selection to issuing for clinical use that mandates a quality management system to yield consistent products.

The necessary quality system applicable at all stages of the process will be addressed in specific documents in development. These include an Aide Mémoire providing guiding principles to health authorities on the appropriate organization and oversight of cell and tissue banking services and to operators on appropriate practices to assure quality (Access to Safe and Effective Cells and Tissues for Transplantation, AM_HCCTASE_07_06), as well as a more detailed guideline for cell and tissue banking.

Many requirements in this field are based on experience and are not supported by robust scientific evidence. As scientific research advances, requirements should move to a stronger evidence base. It is anticipated that this Aide Memoire will be regularly revised and updated with respect to future developments in the field for the benefit of patients.

B. Scope of the document

A shortlist has been constructed of tissue and cell products that are transplanted in the human body and that are used widely in a global context. For each tissue/cell product on the shortlist, a specification has been drafted, defining the essential requirements for the safety and efficacy of that product. The specifications have been drafted by reference to existing international standards and regulations. The short list was agreed at a global consultation with tissue and cell banking experts and regulators held in Ottawa from 29 November to 2 December 2004(1).

The shortlist was constructed by applying the following selection criteria:

- Essential nature of the product for basic healthcare
- Existence of a significant degree of international movement of the product
- Existence of a global commercial market.

Unless otherwise stated, the products referred to are those donated by allogeneic donors.

The shortlist of products for which specifications have been drafted is as follows:

- Frozen Bone and Tendon
- Freeze-dried Bone
- Human skin
- Human Amniotic Membrane
- Cryopreserved Cardiac Valve
- Human Cornea
- Fresh Haematopoietic Stem Cells (unrelated, bone marrow and peripheral blood stem cells)
- Cryopreserved cord blood stem cells (unrelated).

Although there is a global commercial market in the storage of cord blood for family use, and the safety and quality requirements for such activity are equivalent to those outlined here for the shortlist above, this product has not been included in the document due to the lack of evidence of its clinical usefulness.

C. Quality Management Systems

These specifications do not include any description of the quality system that should be applied at all stages from donation to the clinical use of the tissues or cells. All donated human tissues and cells should be retrieved, processed, stored, released and transported following procedures that form part of a comprehensive Quality Management System.

D. Exemptions for Individual Patients according to a Risk:Benefit Assessment

The decision to transplant a tissue or cell product will always be based on a clinical assessment of the risk versus the benefit to the patient, taking any alternative potential therapies into consideration. These product specifications describe the properties, qualities and essential tests required, depending on the type of product under consideration. However, it may exceptionally be judged that a tissue or cell donation not meeting these requirements should be used in transplantation. This may occur, for instance, where the product is likely to have a life-saving impact and alternative options for the treatment of that patient have poor

prognoses. The clinical decision for such exceptions in the interests of informed patients must be made before the tissues or cells are transplanted through mechanisms ensuring good collaboration between national regulatory authorities, tissue bank physicians and clinicians treating patients.

E. PRODUCT QUALITY AND SAFETY GUIDELINES

There are certain general 'cross-cutting' guidelines that apply to all the products included in the short list (Section E.A below). Further criteria apply only to specific HCTT and are detailed separately in the Product Specific Guidelines (Section E.B below). A number of technical terms used below are defined in a glossary in section F of this document.

E.A. Cross-cutting guidelines applying to all HCTT

HCTT should meet the following essential generic guideliness.

E.A.1 Legitimacy of Procurement

Cell or tissue retrieval from a live or a deceased donor must be in compliance with relevant local and national legislation.

Where no relevant legislation exists, cells or tissue should have been altruistically donated under the following circumstances:

- By a live donor who gave unconditional explicit written consent, having been informed of the risks of donation and the testing requirements[1], and the need for follow-up.
- By a deceased donor, who is not known to have objected during his/her life to donating tissue after death. The donor's next of kin may also have agreed to the donation, having been informed of the implications and the testing requirements[1].

Where donation by a live donor requires significant clinical intervention, (e.g. bone marrow or peripheral blood stem cell donation) donations should be taken from unrelated live donors only if they have reached the age of majority. Systems should be in place to ensure that there is clinical follow up of live donors, that the information from this exercise is maintained in a register and that such registers are maintained nationally.

Where the donated tissue is the by-product of surgery being performed for the benefit of the patient, according to an established procedure, and where this tissue would otherwise be discarded as clinical waste, it can be donated by donors of any age applying normal consent procedures (i.e. parents or guardians

[1] For the purposes of adverse event investigation, many countries have deemed it useful that a serum/plasma archive be kept frozen for a number of years after the use or expiry of the tissue.

for under-age donors) and the guidelines for clinical follow-up of the donor for his own safety do not apply.

All personal information will have been stored securely to protect the privacy of donors and donor anonymity will have been ensured.

E.A.2 Donor Selection

The donor's history will have been investigated to exclude the following:

- Clinical, physical or behavioural risk factors for HIV, HBV and HCV
- Familial, iatrogenic or clinical risk factors for TSEs
- Active systemic bacterial[2], viral, fungal or parasitic infections
- Recent exposure to significant infectious risk, including vaccination with a live agent
- Current or past history of malignancy that has been evaluated by the Medical Director (or licensed physician) to be unsuitable for donation due to: significant effects on the cell or tissue type considered for donation; type/extent of treatment; and/or, clinical course of the disease. This exclusion does not apply to basal cell carcinoma, treated in situ cervical carcinoma and certain primary brain tumours or corneal donation for which specific criteria are listed.
- Dementia or neurological disease of unknown aetiology
- Local damage to tissues to be procured
- History of xenotransplantation (i.e. recipients of transplants of live xenogeneic cells, tissues or organs or of human bodily fluids, cells, tissues or organs that have had *ex vivo* contact with live xenogeneic materials unless justified on the basis of a documented risk assessment)
- History of disease of unknown aetiology
- For deceased donors, death from an unknown cause.
- Donor origin or travel history indicates an increased risk of infection with endemic diseases (e.g. HTLV1, Malaria or Chagas), and additional testing or recipient prophylaxis are not appropriate or available. Where the tissues concerned are not vascularized, this exclusion does not apply (i.e. corneas are not included).

For a live donor, the history will have been established and documented by interview with the donor; for a deceased donor, by interview with someone who knew the donor well and review of autopsy results, if one was performed; and for all donors, by a physical examination.

E.A.3 Donor Testing

Testing will have been performed by an authorized or accredited laboratory using validated and, where applicable, licensed tests.

A sample of blood/serum will have been tested for, at least, the following:

[2] Where corneas are stored in organ culture and appropriate microbiological controls are performed, these donors could be accepted according to standard operating procedures or exceptional release procedures.
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- Antibodies to HIV 1 and 2,
- Antibodies to HCV,
- Hepatitis B surface antigen, and
- Syphilis.

Negative or non-reactive results will have been recorded for HIV, HCV and HBV (though note the exceptional situations described in section D).

Where donor origin or travel history indicated an increased risk of infection with endemic diseases, additional testing may have been performed and found negative.

The blood sample used for testing will have been collected as close as possible to the time of donation but definitely within seven days before donation or 24 hours after death (for a deceased donor) or seven days before or after donation (for a live donor)3. The risk of haemodilution before the sample was taken shall have been considered. For cord blood stem cells the maternal blood sample obtained within seven days before or after collection of the CB unit shall be tested for evidence of infection..

For live donors of tissue that can be stored for extended periods, the tissue will have been quarantined until the donor was retested on a sample collected at least 180 days post donation to exclude the possibility of a window period infection, unless more sensitive testing has been performed at donation (e.g. genomic testing for HIV, HCV).

E.A.4 Contamination Control

The time period between death and retrieval and any hold periods before or during processing should be tightly controlled to minimise the proliferation of bacterial contaminants and to preserve the quality of HCTT. The donor body (for deceased donors) and the retrieved HCTT should be held at validated temperature ranges for established periods.

Where tissues or cells cannot be subjected to validated decontaminating or sterilizing treatments, they will have been retrieved and processed following sterile protocols to control contamination and cross contamination. Appropriate samples of tissues will have been cultured for aerobic ,anaerobic bacteria and for fungal contaminants and will have indicated 'no growth' after processing.

Where decontaminating procedures have been applied, they will be validated and will be followed by the culture of appropriate samples, as above. Any processing of tissues or cells following decontamination will have been performed in sterile conditions.

Where terminal sterilization methods have been applied, they will have been validated.

[3] An exception can be made for bone marrow and peripheral blood stem cell donors where the sample can be collected up to 30 days before donation.

Tissues or cells from different donors shall not be pooled during processing unless this is the only way in which clinical efficacy can be achieved on an individual patient basis.

E.A.5 Retrieval and Processing

Retrieval includes the removal acquisition, recovery, harvesting or collection of donor cells and/or tissue.

Processing includes any steps aimed at preserving the required properties of the tissues and cells, decontaminating or sterilizing the tissues or cells or physically modifying the product to facilitate clinical application.

These steps must be performed within a quality management system, documented in standard operating procedures (SOPs), validated to ensure the quality and efficacy of the final product.

E.A.6 Storage, Packaging and Labelling

- The product will be packaged to protect tissue from environmental contamination and to maintain tissue integrity/function during storage and transportation and sealed
- It will be uniquely identified to allow traceability from donor to the transplanting medical professional and subsequently to the recipient.
- It will be labelled to indicate that it contains human tissue and to identify the producing bank .
- The label or package insert will provide clear information on storage, handling and record keeping requirements.
- The label or package insert will indicate the human tissue product type, and description and the product dimensions/volume as appropriate,
- The label or package insert will indicate, if applicable, the presence of sensitizing substances, the preservative used and its concentration, the type and amount of antibiotic or use of irradiation.
- Where tissue has not been sterilized, the decontamination or microbial evaluation procedures applied will be described in the package insert.
- The label or package insert must give clear instructions on the reporting of adverse events associated with the clinical use of the product, and
- The label will indicate an expiry date for the product.

E.B. Product Specific Guidelines

<table>
<tr><td colspan="2">Product

Frozen bone or tendon</td></tr>
<tr><td colspan="2">Full Product Description
Human bone or tendon retrieved from a live (bone only) or deceased donor and stored frozen without manipulation, with or without sterilization by irradiation in its final container</td></tr>
<tr><td>Product-specific donor history exclusions</td><td>Donor Testing</td></tr>
<tr><td>In addition to the cross-cutting guidelines, the following exclusions will apply:

Systemic diseases such as autoimmune or connective tissue disorders, e.g.:
• Rheumatoid arthritis
• Systemic Lupus Erythrematosis
• Polyarteritis nodosa
• Sarcoidosis
• Other systemic autoimmune disease[4]
• Clinically significant metabolic bone disease

For tendons, donors should be under 55 years</td><td>No additional product specific guidelines</td></tr>
<tr><td>Processing</td><td>Storage, packaging and labelling</td></tr>
<tr><td>In addition to the cross-cutting guidelines, the following will apply:

If sterilized by gamma irradiation in its final packaging:
• The product will have an indicator confirming exposure to irradiation
• Product documentation will confirm exposure to the required irradiation dose.[5]</td><td>In addition to the cross-cutting guidelines, the following will apply:

• Documentation available to confirm prior storage at -40^{0}C or lower

• Labelled with an expiry date of 5 years after donation or less</td></tr>
</table>

[4] Donors with a remote history of an autoimmune disease that is no longer symptomatic and is not under treatment shall be acceptable.

[5] This will normally be a minimum absorbed dose of 25kGy for gamma irradiation though a lower dose may be applied where bioburden studies have shown that it achieves the required sterility assurance level of 10^{-6}.

<table>
<tr><td colspan="2">Product

Freeze-dried Bone</td></tr>
<tr><td colspan="2">Full Product Description
Human cortical or cancellous bone retrieved from a live or deceased donor and processed to remove blood and bone marrow, morcellized or shaped and freeze-dried, with or without terminal sterilization</td></tr>
<tr><td>Product-specific donor history exclusions</td><td>Donor Testing</td></tr>
<tr><td>In addition to the cross-cutting guidelines, the following exclusions will apply:

Systemic diseases such as autoimmune or connective tissue disorders, e.g.:
• Rheumatoid arthritis
• Systemic Lupus Erythematosus
• Polyarteritis nodosa
• Sarcoidosis
• Other systemic autoimmune disease [4]
• Clinically significant metabolic bone disease</td><td>No additional product specific guidelines</td></tr>
<tr><td>Processing</td><td>Packaging and labelling</td></tr>
<tr><td>In addition to the cross-cutting guidelines, the following will apply:

Residual moisture less than 6%.
<u>If unsterilized:</u>

• 10% of the processing batch sacrificed for testing for anaerobic and aerobic bacteria and for fungi and found negative
<u>If sterilized in its final container</u>:
• Processed in a controlled, clean environment.
• Indicator confirming exposure to the sterilizing agent.
• Product documentation will confirm exposure to the required irradiation dose.[5]</td><td>In addition to the cross-cutting guidelines, the following will apply:

• The final product will have been stored and transported avoiding excesssively high ambient temperatures (i.e. >30^{0}C)
• Labelled with an expiry date of 5 years after initial processing or less</td></tr>
</table>

<table>
<tr><td colspan="2">Product

Human skin</td></tr>
<tr><td colspan="2">Full Product Description
Human split thickness skin including epidermis and part of the dermis, retrieved from a live or a deceased donor and stored without processing, by cryopreservation or by glycerolisation</td></tr>
<tr><td>Donor history</td><td>Donor Testing</td></tr>
<tr><td>In addition to the cross-cutting guidelines, the following exclusions will apply:

• Dermatitis or fungal diseases of the skin
• Hansen's disease (leprosy)
• Acute or non-healed burns
• Systemic connective tissue disease</td><td>No additional product -specific guidelines</td></tr>
<tr><td>Processing</td><td>Storage, packaging and labelling</td></tr>
<tr><td>In addition to the cross-cutting guidelines, the following will apply:

• Recovered following thorough cleansing of donor site
• Tissue cooled to 2-10^{0}C immediately after retrieval
•
<u>If cryopreserved</u>:
Records available to confirm addition of cryoprotectant and freezing using a validated protocol compatible with the maintenance of the properties required for graft function.
<u>If preserved by glycerolisation</u>:
Records available to confirm addition of glycerol following a controlled protocol</td><td>In addition to the cross-cutting guidelines, the following will apply:

• Evidence available of continuous storage and transportation at 2-10^{0}C for glycerolised skin and at -40^{0}C or lower for cryopreserved.[6]
• Labelled with an expiry date of 5 years after processing or less for cryopreserved tissue, for two years after donation for glycerolised tissue and for 14 days for tissue that has not been subjected to a specific preservation process.</td></tr>
</table>

[6] If cell viability is proven to be critical to graft function,temperatures of -123^{0}C or lower should be used.

<table>
<tr><td colspan="2">Product

Human amniotic membrane</td></tr>
<tr><td colspan="2">Full Product Description
Human amniotic membrane retrieved from a live donor and stored cool without processing, frozen with cell viability preserved (crypreserved), frozen in a glycerol solution without cell viability or dried, with or without terminal sterilization</td></tr>
<tr><td>Donor history</td><td>Donor Testing</td></tr>
<tr><td>In addition to the cross-cutting guidelines, the following exclusions will apply:

• Any complications during the monitoring of the pregnancy which might compromise the tissue quality or safety</td><td>No additional product specific guidelines</td></tr>
<tr><td>Processing</td><td>Storage, packaging and labelling</td></tr>
<tr><td>In addition to the cross-cutting guidelines, the following will apply:
• Recovered from the placenta in aseptic conditions following caesarian section (or clean conditions following vaginal delivery or caesarian section if terminally sterilized) following thorough cleansing of donor site
<u>If cryopreserved</u>:
Records available to confirm addition of cryoprotectant and freezing using a validated protocol compatible with the maintenance of the properties required for cell viability.

<u>If frozen in a glycerol solution</u>:
Records available to confirm addition of glycerol and freezing using a validated protocol compatible with the maintenance of the properties required for graft function.

<u>If air-dried or freeze-dried:</u>
Dried in an aseptic controlled environment to less than 6% residual moisture.

<u>If terminally sterilized</u>:
• Indicator confirming exposure to the sterilizing agent
• Product documentation will confirm exposure to the required irradiation dose.[5]</td><td>Labelled with an expiry date of 2 years after donation for glycerolised tissue, for 5 years if the tissue or cells are cryopreserved and for 14 days for tissue that has not been subjected to a specific preservation process.
Stored at an appropriate temperature, as validated.</td></tr>
</table>

<table>
<tr><td colspan="2">Product

Cryopreserved cardiac valves and vascular segments</td></tr>
<tr><td colspan="2">Full Product Description
Human aortic or pulmonary valve or segment of blood vessel retrieved from a live or deceased donor and cryopreserved.</td></tr>
<tr><td>Donor history</td><td>Donor Testing</td></tr>
<tr><td>In addition to the cross-cutting guidelines, the following exclusions will apply:

• History or evidence of endocarditis, myocarditis, rheumatic and other semilunar valvular disease
• History of coronary artery bypass grafting
• History of cardiomyopathy of viral or idiopathic aetiology
• Donor should have been < 65 years old</td><td>No additional product -specific guidelines</td></tr>
<tr><td>Processing</td><td>Storage, packaging and labelling</td></tr>
<tr><td>In addition to the cross-cutting guidelines, the following will apply:

• Heart or vessels retrieved in clean conditions
• Records available to confirm addition of cryoprotectant and freezing using a validated protocol compatible with the maintenance of the properties required for graft function.</td><td>In addition to the cross-cutting guidelines, the following will apply:

• Stored at -100^{0}C or lower for up to five years[6]
• To avoid the risk of tissue micro-fractures occuring due to rapid warming in the initial thawing phase, instructions should be provided requiring an initial slow warming rate (e.g. room temperature for 5 to 10 minutes or transport in dry ice) of the packaged graft after which rapid warming (e.g. 37^{0}C waterbath) can proceed.</td></tr>
</table>

<table>
<tr><td colspan="2">Product

Human cornea</td></tr>
<tr><td colspan="2">Full Product Description
Human cornea retrieved from a deceased donor</td></tr>
<tr><td>Donor history</td><td>Donor Testing</td></tr>
<tr><td>In addition to the cross-cutting guidelines, the following exclusions will apply:

• Subacute sclerosing panencephalitis
• Congenital rubella
• Reye syndrome
• Leukaemias or lymphomas
• Retinoblastoma or malignant tumours that could affect the anterior segment of the eye
• Receipt of a corneal, scleral or limbal graft
• Active ocular or intraocular inflammation: conjunctivitis, keratitis, scleritis, iritis, uveitis, vitreitis, choroiditis, retinitis.
• Congenital or acquired disorders of the eye that would preclude a successful outcome for the intended use. Tissue with local eye disease affecting the corneal endothelium or previous ocular surgery that does not compromise the corneal stroma is acceptable for use in anterior lamellar or patch grafts. Tissue with local eye disease or previous ocular surgery affecting the corneal stroma that does not compromise the corneal endothelium is acceptable for use in Descemet’s/endothelial grafts.
• Refractive corneal procedures. Tissue from donors with a history of laser photoablation surgery is allowed to be used in cases of tectonic grafting and posterior lamellar procedures</td><td>No additional product-specific guidelines</td></tr>
<tr><td>Processing</td><td>Storage, packaging and labelling</td></tr>
<tr><td>In addition to the cross-cutting guidelines, the following will apply:

• Dissected from the globe in situ or in the laboratory in clean conditions
• examination by slit lamp or transmitted light microscopy to confirm and document presence or absence of</td><td>In addition to the cross-cutting guidelines, the following will apply:

Storage at temperatures within the range specified by SOPs and the manufacturer of the storage, preservation, or culture medium,

Transportation using a packaging method</td></tr>
</table>

defects • Stored by a validated method to preserve integrity and viability	designed to maintain cool storage without freezing Labelled with an expiry date consistent with the recommendation of the manufacturer of the storage, preservation, or culture medium.

<table>
<tr><td colspan="2">Product

Fresh haematopoietic stem cells
(bone marrow or peripheral blood progenitor cells, allogeneic)</td></tr>
<tr><td colspan="2">Full Product Description
Human bone marrow or peripheral blood stem cells retrieved from a live donor and delivered directly for transplantation</td></tr>
<tr><td>Donor history</td><td>Donor Testing</td></tr>
<tr><td>In addition to the cross-cutting guidelines, the following exclusions will apply:

• Any condition that would put the donor at risk during the harvesting procedure
• Sub-acute or progressive multi-focal leucoencephalopathy
• Inherited haematological disorders
• Family history of relevant haematological, immunological or metabolic disease</td><td>In addition to the cross-cutting guidelines, the following will apply:

• HLA typing to be performed by a recognized facility[7]
• CMV testing to be performed on all donations[8]
• ABO and Rh type</td></tr>
<tr><td>Processing</td><td>Storage, packaging and labelling</td></tr>
<tr><td>In addition to the cross-cutting guidelines, the following will apply:

• A nucleated cell count shall be performed after collection.
• For products undergoing manipulation that alters the final cell population, a relevant and validated assay, where available, should be employed for evaluation of the target cell population before and after processing as defined in SOPs
• The results of bacterial and fungal testing must be provided to the transplanting centre[9].</td><td>In addition to the cross-cutting guidelines, the following will apply:

• Stored at 2-10^{0}C
• Labelled with an expiry date and time[10] validated for the temperature of storage and transport according to SOPs and manufacturers' recommendations.</td></tr>
</table>

[7] An HLA typing facility that is accredited, designated, authorized or licensed for that purpose.
[8] CMV positive donations can be used clinically depending on the status of the recipient and the clinical options available for the patient.
[9] Contaminated donations may exceptionally be transplanted where this is judged to be the best option for the patient. Provision of results of bacterial and fungal testing will allow appropriate protective treatment of the recipient.
[10] Where these products are distributed across time zones, the time zone of the collection site should be indicated..

<table>
<tr><td colspan="2">Product

Cryopreserved cord blood stem cells (allogeneic)</td></tr>
<tr><td colspan="2">Full Product Description
Human cord blood collected from the placenta after delivery of the baby and cryopreserved</td></tr>
<tr><td>Donor history</td><td>Donor Testing</td></tr>
<tr><td>In addition to the cross-cutting guidelines, the following exclusions will apply:

• Any condition that would put the donor at risk during the harvesting procedure
• Sub-acute or progressive multi-focal leucoencephalopathy
• Inherited haematological disorders
• Family history of haematological, immunological or metabolic disease</td><td>In addition to the cross-cutting guidelines, the following will apply:

• HLA typing to be performed by a recognized facility[7]
• CMV-IgM specific testing to be performed on all donations[8,11]
• ABO and Rh type</td></tr>
<tr><td>Processing</td><td>Storage, packaging and labelling</td></tr>
<tr><td>In addition to the cross-cutting guidelines, the following will apply:

• A nucleated cell count shall be performed after collection.
• Total nucleated cell count and cell viability shall be performed from >the final cord blood product at the end of processing prior to cryopreservation.
• Retrieved from the placenta in clean conditions
• Processed in aseptic conditions or using closed kits
• Records available to confirm addition of cryoprotectant and freezing using a validated protocol compatible with the maintenance of the properties required for graft function and subsequent storage in liquid or vapour phase nitrogen
• Cell viability shall be verified on a post-thaw sample, prior to release of the unit, on a sample obtained from a contiguous segment of the freezing bag '</td><td>In addition to the cross-cutting guidelines, the following will apply:

• Stored in liquid or vapour phase of nitrogen at temperatures no higher than -123^{0}C

• Labelled with an expiry date validated for the temperature of storage and transport if the product has been thawed before release</td></tr>
</table>

[11] On maternal blood sample obtained within seven days before or after collection of the CB unit

F.Glossary of Terms

The following terms, used in the guidelines, are defined for the purpose of this document only as follows:

Allogeneic	Allogeneic: donated by one person for transplantation to another person
Aseptic processing	Whereby the tissue, container and closure are bacteria-free or subject to sterilization separately and then brought together
Autologous	Removed from and transplanted back to the same person
Clean	Using methods and techniques that keep microbial contamination at a minimum level monitored and controlled
Controlled environment	Restricted work aread of low microbial and particulate content in which non-sterile materials are prepared
Cryopreserved:	Tissue frozen with the addition of, or in a solution containing, a cryoprotectant agent such as glycerol or dimethylsulfoxide
Freeze-dried:	Tissue dehydrated for storage by conversion of the water content of frozen tissue to a gaseous state under vacuum that extracts moisture
Pooling	The physical contact or mixing of cells or tissue from two or more donors in a single container
Processing	Any steps aimed at preserving the required properties of the tissues and cells, decontaminating or sterilizing the tissues or cells or physically modifying the product to facilitate clinical application
Procurement	The process that includes donor identification, consent, donor selection testing and tissue or cell retrieval
Quarantine	The status of retrieved tissue or cells or packaging material isolated physically or by other effective means while awaiting a decision on their release or rejection
Retrieval	Retrieval includes the removal acquisition, recovery, harvesting or collection of donor cells and/or tissue.
Retrieval in Aseptic conditions:	The retrieval of cells and/or tissue using methods that restrict or minimize contamination with microorganisms from the donor, environment, retrieval personnel and/or equipment through the use of sterile gowns, drapes and instruments
Sterilization	A physical or chemical process validated to destroy, inactivate or reduce bacteria and fungi to a Sterility Assurance Level (SAL) of 10-6
Sterilization dose	Minimum absorbed dose of irradiation required to achieve the specified Sterility Assurance Level (SAL).
Tissue decontamination	A validated process that reduces the number of viable bacteria and fungi contaminating a tissue to levels undetectable by conventional culture
Tissue establishment	A tissue bank or a unit of a hospital or another body where activities of procurement, processing, preservation, storage or distribution of human tissues and cells are undertaken, It may also be responsible for procurement or testing of tissues
Traceability	Traceability means the ability to locate and identify the

	tissue/cell during any step between its procurement, processing, testing, storage and distribution, whether to recipient or disposal
Validation	Validation means establishing documented evidence that provides a high degree of assurance that a specific process, piece of equipment or environment will consistently produce a product meeting its predetermined specifications and quality attributes. A process is validated to evaluate the performance of a system with regard to its effectiveness based on intended use.

G. REFERENCES

1. First Global Consultation on Regulatory Requirements for Human Cells and Tissues for Transplantation Ottawa, 29 November to 1 December 2004 - WHO publication no.
ISBN 92 4 159329 6.

Documents included in the review

International Atomic Energy Agency

International Standards on Tissue Banks - Final version

http://www.int-tissuebank.com/

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**)

European Union

Directive 2004/23/EC (entered into force 7th 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) 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)

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, number101: 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)

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

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)

Australian Therapeutic Goods Administration (TGA)

Code of Good Manufacturing Practice – Human Blood and Tissues, August 2000. (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)

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)

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)

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)

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)

Eye Bank Association of America (EBAA)
Medical Standards. (Can be ordered at: http://www.restoresight.org/general/medstndprocedureman.pdf)

Health Canada
Directive and Guidance Document.
(http://www.hc-sc.gc.ca/hpfb-dgpsa/bgtd-dpbtg/cto_directive_e.html)