International Atomic Energy Agency

THE IAEA PROGRAMME IN RADIATION AND TISSUE BANKING

International Standards on Tissue Banks

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INTRODUCTION

A) International Standards for Tissue Banks

Standards have been established by the IAEA that ***should*** be used as a starting point for Good Tissue Banking Practices. These Standards describe the safety and quality dimensions of human tissue ***for*** transplantation, Quality ***Management, processing method, tissue sterilization and validation. These Standards apply to all types of tissues, including corneas and to cells (see Definitions).***

B) Guide for Legal and Regulatory Control

In order for a Tissue Banking Programme to be successfully ***implemented, there*** is need for a variety of ***Laws and Regulations*** to be legislated and enforced. These ***Laws and Regulations*** should cover the safety of the tissue to recipients as well as ethical concerns such as maintaining the dignity of the donor and his/her family and ***respect the gratuity of the donation. Regulations*** should be based on Standards adopted by the country, individual Tissue Banks or associations representing Tissue Banks in the specific country/area. An International or Intergovernmental approach to the development of Laws and Regulations is suggested for those areas of ***the world*** that have common legal systems, eliminating redundant or conflicting Regulations.

In the International Atomic Energy Agency's view, this Guide for Legal and Regulatory Control shall present requirements in a form that can be used for establishing Tissue Banks and determining whether a Tissue Bank complies with current Good ***Tissue Banking*** Practices. It shall also serve as an aid for interpreting and clarifying the Standards. It is also intended to support the harmonisation of inspection and internal audit procedures.

The reasons for the justification of ***this Guide for*** Legal and Regulatory Controls are clear: there is need to protect the health and well-being of the citizens, encourage cost-effective and improved healthcare, promote social programmes that work for the well being of the community, prohibit unethical ***practices, avoid*** health hazards associated with the distribution and transplantation of tissues ***and to protect against Tissue Banks that refuse to adhere to acceptable practices.***

The document is divided in two parts:

Part 1: ***International Standards for Tissue Banks***

The Standards ***include*** two sections. Section A deals with general and organisational policies. Section ***B deals*** with the implementation of these policies.

Part 2 ***Guide for Legal and Regulatory Control***

Part 2 includes a Guide which advises regulatory bodies about the aspects which must be considered in setting up a regulatory system and evaluating compliance with the ***system***.

TABLE OF CONTENTS:

Nervous System: Evaluation of a Suitable Donor. ***Reference List***

Part 1: ***INTERNATIONAL STANDARDS FOR TISSUE BANKS***

Section A: General and Organisational Policies

A 1.000 Introduction

A 1.100 General

A 1.110 Scope

These Standards applies to human tissues used for therapeutic purpose, excluding reproductive and genetically modified tissues. It does not apply to animal tissues.

A 1.120 Purpose of the ***Standards***

These standards brings together current ***State of the Art practice*** on selection of donors, tissue retrieval, testing, processing, storage, ***labelling and distribution of finished tissue,*** in order to provide safe tissue of reliable quality while respecting the ethical rules.

A 1.130 Concerns

The therapeutic use of tissues raises ethical and safety concerns.

Safety of tissues includes the following aspects:

- ***Avoiding transmission of communicable diseases including bacteria, parasites, viruses, prions and of tumours;***
- ***Avoiding adverse events due to additives and residues from chemical or physical methods of processing;***
- ***Preserving efficient biological qualities and assuming reproducibility and traceability.***

Besides bacterial and parasitic infection, several cases of viral disease(*) and Creutzfeldt-Jakob (**) diseases transmission have been reported in the literature. These events should be compared with the thousands of patients that have received tissues

successfully, but imply the need for preventive measures.

Not only the risks, but also the risk-benefit balance has to be considered. Risks include known risks, which imply preventive measures and unknown risks, which call for precautionary measures. On the other side, the benefit and the existence or absence of alternative treatments should be appreciated.

The factors of clinical safety are well known and include donor selection, retrieval ***conditions***, processing protocol and controls, ***distribution protocol, traceability*** and record keeping, including proper indication, surgical technique and postoperative care.
* ***(Two cases of HIV, three of Hepatitis B and two of Hepatitis C)***
** ***(Three cases through corneas and more than sixty through non- viable freeze-dried dura-mater)***

A 1.200 Definitions
See Annex 1

A 2.000 Ethical and Legal Rules

A 2.100 General
In each country, the applicable Inter-governmental, National, Regional and Local Law or Regulation governing consent and retrieval of tissues from living or cadaver donors shall be followed.

Recommendations about the Ethical aspects of the use of human tissues for therapeutic purpose have been published by the World Health Organisation (WHA 44.25 - May 1991) and Council of Europe (78-29 May 1978). Council of Europe also adopted a Convention on the Human Rights and Biomedicine (Oviedo 4 April 1997) and is preparing an Additional Protocol to the Convention on Transplantation of Organs and Tissues of Human Origin.

Recommendations about the safety aspects of Tissue Banking were also adopted by the Council of Europe (Recommendation No R (94) 1 on Human Tissue Banks) and by the European Group on Ethics in Science and New Technologies to the European Commission (Opinion on Ethical Aspects of Human Tissue Banking, adopted on 21 July 1998).

A 2.200 Permission for Tissue Retrieval

If there is no applicable Inter-governmental, National, Regional and Local Law or Regulation, the following principles shall be applied:

A 2.210 Living Donor Consent

A 2.211 Voluntary Donation of ***Tissue***

- Appropriate medical investigation shall be made to evaluate and reduce the risk to the health of donor and recipient.

- The donor must be given appropriate information before the removal about the possible consequences of this removal, in particular medical, social and psychological, as well as the importance of the donation for the recipient. An ***Informed Consent in writing*** shall be obtained from the living donor. Consent before an official body may be necessary according to ***applicable*** Inter-governmental, National, Regional and Local Law or Regulation.

- In case of a minor or otherwise legally ***incapacitated person, Informed*** Consent shall be obtained from his legal representative, if the donor does not object to it. ***The appropriate authority shall be consulted in accordance*** to ***applicable*** Inter-governmental, National, Regional and Local Law or Regulation.

- ***The*** donation of substances, which cannot regenerate, is usually confined to transplantation between family related persons and restricted to major and capable persons.

A 2.212 Collection of Surgical Residues

- Surgical residues are collected during a surgical procedure where the material is ***collected*** for therapeutic purpose other than to obtain tissue ***(e.g. femoral head, skin and amnion)***.

- Informed Consent shall be obtained from the donor according to applicable Regulation.

A 2.220 Non-Living Donor Consent

- ***No removal of tissue*** will take place when there ***was*** an open or presumed objection on the part of the deceased.

- Permission or confirmation of the absence of objection for tissue donation shall be obtained from the next of kin.

- In case of a minor or legally ***incapacitated*** person, the consent of his legal representative is required.

- ***Removal of tissue*** can be effected if it does not interfere with a forensic examination or autopsy as required by Law.

A 2.230 Consent Documentation

Consent for tissue donation shall be documented. The consent form shall specify whether there is a general permission for organs and / or tissues or permission for specified organs and / or tissues only.

A 2.300 Monetary Inducement for Donation

A 2.310 Prohibition of Payment to Donor

Monetary payment or advantages for the donation shall not be made to living donors, cadaver donor's next of kin or any donor-related party.

A 2.320 Compensation for Donation-Related Expenses

Donors or their family shall not be financially responsible for expenses related to retrieval of tissues.

A 2.400 Anonymity

Anonymity between donor and unrelated recipient shall be strictly preserved. Anonymity between donor and recipient shall allow tracking of tissues, through anonymous identification numbers.

A 3.000 Organisation of a Tissue Bank

A 3.100 Institutional Identity

A 3.110 General

The purpose of a Tissue Bank shall be clearly established and documented. The Tissue Bank shall state whether it is a free standing entity or part of an Institution.

A 3.120 Authorisation, Licensing or Registration

The Tissue Bank shall comply with all applicable Inter-governmental, National, Regional and Local Law or Regulation for authorisation, licensing ***or*** registration.

A 3 130 Collaboration with other Organisations

A 3. 131- Written Agreement – Contract

Each Tissue Bank shall have written agreements or contracts with all other organisations, which perform donor screening services, tissue retrieval, processing or distribution ***for the Tissue Bank.***

Tissue Banks which contract for laboratory services shall verify the laboratory licensing or accreditation, according to applicable Inter-governmental, National, Regional and Local Law or Regulation.

A 3. 132 On-site Audit

The Tissue Bank shall maintain documentation, which is audit-specific for the services performed for the Tissue Bank. Such documentation shall itemise all operational systems, which were audited to determine compliance with Standards or applicable Regulation.

A 3.200 Personnel

A 3.210 Medical Director

A 3.211- Qualification

The Medical Director shall be qualified by training and experiences for the scope of activities being pursued in accordance with applicable Inter-

governmental, National, Regional and Local Law or Regulation.

A 3.212- Responsibilities

The Medical Director shall be responsible for medical operations, including compliance with these Standards. ***His/Her responsibilities include determining*** what tissues are to be collected, define donor screening policies and prescribe technically acceptable means for their processing, Quality Assurance, storage and distribution. The Medical Director shall be responsible for policies and procedures regarding donor suitability and adverse ***events***.

A 3.213-Medical Advisory Board

It is recommended that a Tissue Bank set up a Medical Advisory Board to provide medico-technical and scientific advice (external from the Tissue Bank).

A 3.220 Administrative Director

The Administrative Director, ***when*** applicable, ***shall*** be responsible for administration, ***management, and other general activities. The Administrative Director shall not be responsible for medical activities.***

A 3.230 Staff

A 3.231 General

The Tissue Bank shall have sufficient personnel for pursuing the various tasks.

A 3.232 Qualification

The Tissue Bank staff must possess the educational background, experience and training, sufficient to assure assigned tasks are performed in accordance with the Tissue Banks established procedures.

A 3.233 Responsibilities

The technical staff shall be responsible for implementation of policies and procedures as established by the Medical Director. ***The duties*** of each staff member shall be described ***in a written*** job description. Staff must demonstrate competency in operations to which they are assigned.

A 3.240 Training

The scope of activities, specific staff responsibilities and ***reporting structure shall*** be established by the Medical Director. The Medical Director shall ensure that all staff members have adequate training to perform their duties safely and competently. The Medical Director shall be responsible for ensuring that technical staff maintains their competency by participation in training courses and technical meetings or other educational programmes. All staff shall review applicable institutional policies and procedures annually and when changes are made.

A 3.300 Quality Management System

In order to reduce the risk for patients by the transplantation of tissues to an acceptable level, it is necessary to operate an effective Quality Management System.

The System may include extensive testing of donor blood and tissue samples, but this alone is not sufficient guarantee of safety and efficacy and the System should include other management and control measures.

Those involved in procuring, processing and supplying tissues for transplantation shall In addition, a risk analysis of procedures prone to error to disease transmission should be used to develop safe procedures implement a Quality Management System based on clearly identified requirements for tissues.

A 3.310 Quality Requirements

The Quality Requirements form the basis of all Quality Assurance and ***Quality Control*** Programmes. It is necessary to define the Quality Requirements not only for the final product, but also for the starting material collected, reagents and equipment used, staff competencies, testing techniques, packaging materials, labels and process intermediates.

These Quality Requirements are best prescribed and quantified in written specifications. These specifications determine the Quality Control testing or

inspection performed on which release decisions are based.

The Quality Requirements will be based on characteristics that effect both patient safety and maintaining the clinical effectiveness of the product.

A 3.320 Quality Management

It is recognised that quality has to be managed in an organisation and that a systematic approach is the only way to ensure that the quality of products produced and services delivered consistently meets the Quality Requirements. The high level of Quality Assurance required for safety, critical therapeutic medical products and clinical services can only be achieved through the implementation of an effective Quality Management.

The International Standard for Quality Management is the ISO 9000 series. Specific principles to be incorporated into the Quality Systems covering the manufacture and Quality Control of medicines are known as Good Manufacturing Practice(GMP). The ISO Standards, GMP or other applicable Standards and other applicable Inter-governmental, National, Regional and Local Law or Regulation, should be consulted when developing a Quality Management for Tissue Banking organisations and other procurement organisations.

A 3.330 The Basic Elements of an Appropriate ***Quality Management System***

A 3.331 Organisational Structure and Accountability

- This is necessary to achieve the Quality Requirements and for reviewing the effectiveness of the arrangements for Quality Assurance. There should be a suitably qualified and experienced member of staff appointed who verifies that the Quality Requirements are being met, and that there is compliance with the Quality ***Management System***.

- The Quality Manager should be a designated individual who should be independent of production

(not directly responsible for or involved in the procurement, ***processing and testing of tissue)***

and preferably of other responsibilities within the Tissue Bank.

The Quality Manager should be generally familiar with the specific work being reviewed and be responsible for each Quality Assurance review. This individual should report, for his function, specifically ***to this Medical Director and/or his/her designee.***

Where a Tissue Bank is operated within a large organisation with its own Quality Department and possibly its own Quality ***Manager*** then strong working links should exist between the Tissue Bank's Quality ***Manager*** and the relevant Quality Department staff, as well as to the ***Medical Director***.

A 3.332 Documentation

- Rationale

  The objectives of thorough documentation are to define the system of information and control, to minimise the risk of misinterpretation and error inherent in oral or casually written communication and to provide unambiguous procedures to be followed.

  Documents should clearly state the Quality Requirements, organisational structures and responsibilities, the organisation's policies and standards, the management and technical procedures employed and the records required.

- General

  All procedures in the processing of tissue should be documented and the documents controlled

  Documentation should be legible, readily identifiable and retrievable

  Documentation should clearly identify the way in which it is to be used and by whom

Documentation should be available to staff to cover all procedures

Any correction should be handwritten clearly and legibly in permanent ink and signed and dated by an authorised person

- Control of Documentation

  The system for document control should identify the current revision status of any document and the holder of the document

  The system in place should demonstrate that all controlled documents meet the following criteria:

  - they are current and authorised
  - they are reviewed at regular intervals
  - multiple copies are controlled with a distribution list
  - obsolete documents are removed and controlled to prevent further use
  - changes to documents should be acted upon promptly. They should be reviewed, dated and signed by the authorised person and formally implemented

- Storage and Retention of Documentation

  Documented procedures should be established and maintained for identification, collection, filing, storage, retrieval and maintenance of all documents

  Master copies of obsolete copies should be archived in a secure and safe ***environment for 10 years or in accordance with applicable Inter-governmental, National, Regional and Local Law or Regulation.***

A 3.333 Control of Processes (SOPs)

- Written instructions of Standard Operating Procedures (SOPs) shall be produced where it is essential that ***tasks must be*** performed in a consistent way. Equipment, processes and

procedures shall be validated as effective before being implemented or changed.

Equipment essential to the quality of the product shall be routinely serviced and calibrated, if appropriate. The processing environment and staff performing processes shall meet minimum, prescribed Standards of cleanliness and hygiene.

- The Tissue Bank shall maintain a SOPs Manual which details in writing all aspects of ***these Standards.*** The SOPs shall be utilised to ensure that all material released for transplantation meet at least minimum requirements defined by professional Standards and applicable Inter-governmental, National, Regional and Local Law or Regulation.

  The ***SOPs*** Manuals should include, where relevant, but should not be limited to the following:

  - Standard procedures for donor screening, consent, retrieval, processing, preservation, testing, storage and distribution
  - Quality Assurance and Quality Control Policies
  - Laboratory procedures for tests performed in-house and in contracted laboratories
  - Specifications for materials used including supply, reagents, storage media and packaging materials
  - Personnel and facility safety procedures
  - Standard procedures for ***facility*** maintenance, cleaning and waste disposal procedures
  - Methods for verification of the effectiveness of sterilisation procedures
  - Equipment maintenance, calibration and validation procedures
  - Environmental and microbiological conditions and the methods used for controlling, testing and verification
  - Physiological and physical test specifications for materials
  - Methods for determination of shelf life, storage temperature and assigning expiry dates ***of tissues***
  - Determination of insert and or label text

- Policies and procedures for exceptional release of material

- Procedures for adverse events reporting and corrective actions
- Donor/recipient tracking and product recall policies and procedures.

- ***All SOPs, their modification and associated*** process-validation studies shall be reviewed and approved by either the Medical or Administrative Director as dictated by content. All medically related SOPs shall be reviewed and approved by the Medical Director.

  Copies of the SOPs Manual shall be available to all staff, and to authorised individuals for inspections upon request. Upon implementation, all SOPs shall be followed as written. SOPs shall be updated at regular intervals to reflect modifications or changes. The authorised person, depending on the content shall approve each modification ***or change.***

  Appropriate training shall be provided to pertinent staff. Obsolete ***SOPs*** Manuals shall be archived for a minimum of 10 years taking into account the shelf life of the material.

A 3.334 Record Keeping

- ***General***

  Records shall be confidential, accurate, complete, legible and indelible. All donor, processing, storage, and distribution records should be maintained for 30 years or in accordance with applicable Inter-governmental, National, Regional and Local Law or Regulation.

  Records shall hold all information that identifies the origins of the product and to demonstrate that the product meets all the Quality Requirements. Records shall show that all the required processing steps and all Quality Control tests have been performed correctly by trained staff and that the

product has only been released for use after the correct authorisation.

Records shall also demonstrate correct handling and storage of materials and track the ***final status of*** products, whether transplanted, discarded or used for research. The use and storage of records shall be controlled.

- Contract Records

  When two or more Tissue Banks participate in tissue procurement, processing, storage or distribution functions, the relationships and responsibilities of each shall be documented and ensure compliance ***with relevant scientific and quality professional Standards*** by all parties. Tissue Banks should perform on-site audits of contract laboratories to ensure their compliance with ***relevant scientific and professional Standards,*** Technical Manuals and the Tissue Bank's own requirements.

- Donor Tracking

  Each component shall be assigned one unique identifier that shall serve as a lot number to identify the material during all steps from collection to distribution and utilisation. This unique number shall link the final packaged material to the donor. This number shall be used to link the donor to all tests, records, organs and other material, and for tracking purposes to the recipient.

  Records shall include identification and evaluation of the donor, blood testing and micro-biological evaluation of the donor, conditions under which the material is procured, processed, tested and stored and its final destination.

  Records shall indicate the dates and identity of staff involved in each significant step of the operation.

- Inventory

  A record of unprocessed, processed, quarantined and distributed tissues shall be maintained.

- Recipient Adverse Events and Non-compliances

  An adverse events file shall be maintained including any non-compliance.

- Electronic Records

  If a computer record-keeping system is used, there shall be a system to ensure the authenticity, integrity and confidentiality of all records but retain the ability to generate true paper copies.

  A description of the system, its function and specified requirements must be documented. The system shall ***record the identity of persons*** entering or confirming critical data.

  Alteration to the system or programme shall only be made in accordance with defined procedures. When the release of finished batches is conducted by computerised systems it must identify and record the person (s) releasing the batches.

  Alternative management systems should be available to cope with failures in computerised systems.

A 3.340 Methods for Detecting, Correcting and Preventing Quality Failures from Recurring

A 3.341 Quality Failures

Quality failures include in-use product deficiencies (complaints, adverse events, etc.), failures to meet Quality Control specifications and non-compliance with procedures. Methods for detecting failures include Quality Control tests, inspections, Quality Audits***, staff and end-user feedback***. The ability to trace, locate, quarantine and recall materials, ***consumables and products at any stage, is essential to patient safety.*** Serious failures shall be thoroughly registered, investigated and appropriate changes to specifications, systems and

procedures implemented to prevent further failures of a similar nature.

A 3.342 Audit

The Tissue Bank shall participate in an Audit Programme. Quality Assurance staff shall perform internal audits. Focused audits shall be conducted to monitor critical areas and when problems with quality have been identified. Regular audits shall be performed by ***qualified staff*** who do not have direct responsibility for the processes being audited.

A 3.350 Competency

The educational and training requirements for each member of staff shall be determined and specified. There shall be regular and formal appraisal of staff competency. Training and education shall include the requirements for quality, **Standards of Practice and Good Hygiene** as well as appropriate continuing professional development. ***Records of training shall be maintained up to date.***

A 3.400 Facilities and Equipment

A 3.410 General

The facilities of the Tissue Bank shall be of suitable size and location and shall be designed and equipped for the specialised purposes for which they are to be used.

A 3.420 Design

The design of the ***facilities*** shall prevent errors and cross-contamination. Critical procedures shall be performed in designated areas of adequate size.

A 3.430 Security

Access to the Tissue Bank shall be limited to authorised persons.

A 3.440 Environmental Monitoring

Environmental monitoring procedures shall be established, when appropriate, as part of the Quality Assurance Programme. The procedures shall include acceptable test parameters. The monitoring may include particulate air samplings and work surface cultures. Each monitoring activity shall be documented.

A 3.450 Sanitation

Facilities used for retrieval, processing or preservation, where there is potential for cross-contamination of material or exposure to blood-borne pathogens, shall be subjected to routine, scheduled and documented cleaning procedures.

A 3.460 Equipment and Instruments

Equipment and instruments shall be of appropriate quality for their intended function. Equipment and non-disposable supplies that come into contact with ***tissue shall be*** constructed so surfaces do not alter the safety or quality of the material.

Equipment shall be designed, manufactured and qualified for appropriate cleaning and shall be sterilised or decontaminated after each use. Multiple uses of ***disposable instruments*** for several donors shall be excluded.

There shall be SOPs for monitoring, inspection, maintenance, calibration, and cleaning procedures for each piece of equipment. ***Storage equipment*** shall be inspected on a regularly scheduled basis. Appropriate certification and maintenance records shall be maintained for ***equipment and instruments***.

A 3.470 Environmental Safety

A 3.471 General

Each Tissue Bank shall provide and promote a safe work environment by developing, implementing and enforcing safety procedures. Safety precautions and procedures for maintaining a safe work environment shall be included in the ***SOPs*** Manual and shall conform to applicable Inter-governmental, National, Regional and Local Law or Regulation.

A 3.472 Safety Procedures

Safety procedures shall include, but are not limited to the following:

- Instructions for fire prevention and evacuation routes in case of fire or natural disaster

- Procedures for prevention of worker injury including possible exposure to biohazards material
- Procedures for proper storage, handling and utilisation of hazardous materials, reagents and supplies
- Procedures outlining the steps to be followed in cleaning biohazard spills
- Hazardous material training including chemical, biological and radioactive hazards
- Immunisation: appropriate vaccinations should be offered to all non-immune personnel whose job-related responsibilities involve potential exposure to blood-born pathogens. Personnel files should include documentation of receipt of vaccination or refusal of vaccination
- Personnel: personnel engaged in the retrieval, processing, preservation and packaging of tissues shall be suitable attired to minimise the spread of transmissible pathogens among and between donors, tissue and staff. Any staff member with a serious infectious condition shall be excluded from the Tissue Banking activities until the condition is resolved.

A 3.473- Waste Disposal

Human tissue and other hazardous waste items shall be disposed of in such a manner so as to ***prevent hazards*** to Tissue Bank personnel or the environment and shall conform to applicable Inter-governmental, National, Regional and Local Law or Regulation. Dignified and proper disposal procedures shall be applied to human remains.

Section B: Implementation

B 1.0 00 Donor Selection

B 1.1 00 General

The suitability of a specific donor for tissue allograft donation is based upon medical and behavioural history, medical records review, physical examination, cadaveric donor autopsy findings (if an autopsy is performed) and laboratory tests.

B 1.2 00 Medical and Behavioural History

B 1.2 10 Donor History Review

Donor evaluation includes an interview of the potential living donor or the cadaveric donor's next of kin, performed by suitably trained personnel, using a questionnaire.

A qualified physician shall approve donor evaluation.

B 1.2 20 Exclusion Criteria

B 1.2 21 General Contraindications

The following conditions contraindicate the use of tissues for therapeutic purposes:

- History of chronic viral Hepatitis.
- Presence of active viral Hepatitis or jaundice of unknown etiology.
- History of, or clinical evidence, or suspicion, or laboratory evidence of HIV infection.
- ***Risk factors for HIV, HBV and HCV have to be assessed by the Medical Director according to existing National Regulations taking into account national epidemiology. Annex 2 includes a generally agreed list of risk factors.***

- Presence or suspicion of central degenerative neurological diseases of possible infectious origin, including dementia (e.g. Alzheimer's

  Disease, Creutzfeldt-Jakob Disease or familial history of Creutzfeldt-Jakob Disease and Multiple Sclerosis).

- Use of all native human pituitary derived hormones (e.g. growth hormone), possible history of dura-mater allograft, including unspecified intracranial surgery.

- ***Septicemia*** and systemic viral disease or mycosis or active tuberculosis at the time of procurement ***preclude procurement*** of tissues. In case of other active bacterial infection, tissue may be used only if processed using a validated method for bacterial inactivation and after approval ***by the*** Medical Director.

- Presence or history of malignant disease. Exceptions may include primary basal cell carcinoma of the skin, histologically proven and unmetastatic primary brain tumour (see annex 3).

- Significant history of connective tissue disease (e.g. systemic lupus erythematosus and rheumatoid arthritis) or any immunosuppressive treatment.

- Significant exposure to a toxic substance that may be transferred in toxic doses ***or damage the tissue*** (e.g. cyanide, lead, ***mercury and*** gold)

- Presence or evidence of infection or prior irradiation at the site of donation.

- Unknown cause of death
  If at the time of death the cause of death is unknown, autopsy shall be performed to establish this cause.

B 1.2 22 Specific ***Tissue*** Selection Criteria

Cornea donors with solid extra-ocular malignancies are generally accepted.

B 1.3 00 Physical Examination

Prior to procurement of tissue, the donor body shall be examined for general exclusion signs and for signs of infection, trauma or medical intervention over donor sites that can affect the quality of the donated tissue.

B 1.4 00 Cadaveric Donor Autopsy Report

If an autopsy is performed, the results shall be reviewed by ***the Medical Director*** or designee before tissue is released for distribution.

B 1.5 00 Transmissible Diseases Blood Tests

B 1.5 10 General

B 1.5 11 Law and Practice

Tissues shall be tested for transmissible diseases in compliance with Law and practice in the country concerned. In the case of living donors, applicable consent procedure for blood testing shall be followed.

B 1.5 12 Tests

Tests shall be performed and found acceptable on ***properly identified*** blood samples from the donor using recognized, and if applicable, licensed tests and according to manufacturer's instructions. Tests shall be performed by a qualified, and if applicable, ***licensed laboratory and according to Good Laboratory Practice (GLP).***

B 1.5 13 ***Timing*** of Blood Sampling

Blood for donor testing should be drawn at or within seven days of the donation and preferably within 24 hours after death.

B 1.5 14 Recent Blood Transfusion

For potential tissue donors who have received blood, blood components, or plasma volume expanders within 48 hours prior to death, if there is an expected hemodilution of more than 50%, based on calculation algorithm (see example of algorithm

in Annex 4), a pre-transfusion blood sample shall be tested.

B 1.5 15 Notification of Confirmed Positive Test Results

The living donor or cadaver ***donor's*** next of kin or physician shall be notified in accordance with State Laws of confirmed positive results having clinical significance.

Confirmed positive donor infectious disease tests shall be reported to Local/National Health Authorities, ***when required***.

B 1.5 16 Donor Serum Archive

A sample of donor serum shall be securely sealed and stored frozen in a proper manner until 5 years after the expiration date of the ***tissue or according to applicable Inter-governmental, National, Regional and Local Law or Regulation.***

B 1.5 20 Blood Tests

B 1.521 Minimum Blood Tests

Minimum Blood Tests shall include:

- *Human Immunodeficiency Virus Antibodies (HIV-1/2-Ab)*
- *Hepatitis B Virus Surface Antigen (HBs-Ag)*
- *Hepatitis C Virus Antibodies (HCV-Ab)*
- *Syphilis:* ***nonspecific (eg. VDRL) or preferably specific (eg. TPHA)***

B 1.522 Optional Blood Tests

Optional Blood Tests could be necessary for compliance with applicable Inter-governmental, National, Regional and Local Law or Regulation ***and/or to screen for endemic diseases:***

- Hepatitis B ***core antibodies*** (HBc-Ab): ***HBc-Ab*** should be negative for tissue validation. Though, if the HBc-Ab test is positive and the HBs-Ag is negative, confirmation cascade should be entered.

  If the antibodies against the surface antigen are found (HBs-Ab), the donor can then be considered

to ***have been*** recovered from an infection and the tissue can be used for transplantation.

- Antigen test for HIV (p24 antigen) or HCV or validated Molecular Biology Test for HIV and HCV (e.g. PCR), if performed by an experienced laboratory.

- Antibody to HTLV 1: depending on the prevalence in some regions

- Cytomegalovirus (CMV), Ebstein-Barr Virus (EBV) ***and*** Toxoplasmosis Antibodies: for immunosuppressed patients

- Alanine Aminotransferase (ALT) for Living Donors:
  In addition to the general testing requirements, testing living donors of tissue for Alanine Aminotransferase (ALT) is recommended.

B 1.523 Living Donors Retesting

Retesting of living donors for HIV and HCV at 180 days is recommended. If another method of ***increasing*** safety, rather than retesting ***(antigen testing, Molecular Biology or viral inactivation method)*** is used (and allowed by applicable Regulation), it shall be documented and validated.

B 1.5 30 Exclusion Criteria

B 1.531 ***General Exclusion Criteria***

Positive results for HIV, Hepatitis and HTLV-1 are reasons for exclusion.

B 1.532 ***Specific Exclusion Criteria***

In life threatening situations for the recipient (e.g. related HPC donation), positive results for Hepatitis ***are no reason for exclusion***, in accordance to applicable Regulations. In these situations, ***tissues*** with a higher risk for recipient may be offered as long as full information is given to the recipient or, if it is not possible, to his relatives.

B 1.6 00 Bacteriological Studies of Donor and Tissues

B 1.6 10 Bacteriological Testing Methods

Representative samples of each retrieved ***tissue*** have to be cultured, if the tissues are to be aseptically processed without terminal sterilisation. Samples shall

be taken prior to exposure of the tissue to antibiotic containing solution.

The culture technique shall allow for the growth of both aerobic and anaerobic bacteria as well as fungi. Results shall be documented in the donor record.

Blood culture, if procurement is performed on a cadaver donor, may be useful in evaluating the state ***of the*** cadaver and interpretating the cultures performed on the grafts themselves. They shall be reviewed by the ***Medical Director*** or designee.

B 1.6 20 Bacteriological Bioburden Limits

If bacteriological testing of tissue samples obtained at the time of donation reveals growth of low virulence microorganisms, which are commonly considered nonpathogenic, the tissue may not be distributed without being further processed in a way that effectively decontaminates the tissue.

Tissue from which high virulence microorganisms have been isolated are not acceptable for transplantation, unless the procedure has been validated to effectively inactivate the organisms without harmful potential effects, taking in account possible endotoxins.

B 1.7 00 Non Microbiological Tests

Non-microbiological tests depend upon the tissues and cells to be transplanted.

Haematopoeitic Progenitor Cell donor ***selection requires as a minimum:***

- ABO Blood Group ***and*** Rhesus Group
- Human Leucocyte Antigen Typing (HLA)
- ***Whole Blood Cell Count***

B 1.8 00 Age Criteria

Donor age criteria for each type of tissue shall be established and recorded by the Tissue Bank.

B 1.9 00 Cadaver Donor Retrieval Time Limits

Tissues shall be retrieved as soon after death as is practically possible. Specific time limits vary with each tissue obtained, which shall be determined by the ***Medical***

Director. Usually, procurement of tissues should be completed within 12 hours after death (or circulatory arrest if also an organ donor). If the body has been refrigerated within 4 to 6 hours of death, procurement should preferably start within 24 hours and no later than 48 hours.

B 2.0 00 Tissue Retrieval

B 2.1 00 Rationale

There shall be documented procedures, which detail all requirements for retrieval to ensure that these processes are carried out under controlled conditions.

Retrieval shall be performed using techniques appropriate to the specific tissue recovered, taking into consideration the eventual utilisation of the tissue.

B 2.2 00 Non-Living Donor Tissue Retrieval

B 2.2 10 Determination of Death

Tissue Bank physicians or physicians involved in removal or transplantation shall not pronounce death nor sign the death certificate of any individual from whom tissue will be collected.

Inter-governmental, National, Regional and Local Law or Regulation concerning determination of death shall be respected.

B 2.2 20 Donor Identification

Precise identification of the cadaver donor shall be performed before procurement begins.

B 2.2 30 Retrieval Conditions

B 2.2 31 Facility for Retrieval

Procurement shall be accomplished in an operating room or adequate mortuary facility.

B 2.2 32 Procurement Equipment Sterility

All instruments and equipment used for procurement shall be sterilised between procurements.

B 2.2 33 ***Aseptic or Clean/Non-Sterile Procurement Techniques***

Tissues may be removed using either aseptic or ***clean/non-sterile procurement techniques***:

- ***Aseptic technique***:

  Aseptic technique shall be observed throughout the procurement procedure. Procurement sites shall be prepared using ***a standard surgical technique;*** all methods shall be consistent with standard operating room practice.

- ***Clean/non-sterile*** technique:

  Allografts procured using ***clean/non-sterile*** *techniques* are suitable for transplantation, if efficient validated sterilising methods are used to eliminate pathogens after retrieval.

B 2.2 34 Samples for Microbiological Testing

Samples for microbiological testing shall be taken, where applicable.

B 2.2 40 Body Reconstruction

Following tissue procurement, the donor's body is to be reconstructed to closely approximate its original anatomical configuration and to make usual funeral proceedings possible.

B 2.3 00 Surgical Residues Collection

Surgical residues shall be collected under aseptic conditions during a surgical procedure in the operating theatre.

B 2.4 00 Living Donor Tissue Retrieval

Tissues must be removed under conditions representing the least possible risk to the donor, in properly equipped and staffed institutions.

B 2.5 00 Packaging and Transportation to the Tissue Bank

B 2.5 10 Procurement Container

- Each tissue segment shall be packaged individually as soon as possible after retrieval, using sterile containers in a manner, which will prevent contamination.

- Containers shall conform to Inter-governmental, National, Regional and Local Law or Regulation, as appropriate.

- Proper reagents or preservation solution shall be used, as specified in SOPs

- Procedures shall be used for ensuring and documenting proper temperature storage during transit.

B 2.5 20 Procurement Container Integrity

After filling and closing the container, it shall not be re-opened nor the tissue removed until further processing by the Tissue Bank.

B 2.5 30 Procurement Container Label

- At all times, the container shall be labelled with the donor and tissue identification, in such manner that traceability of tissues will be achieved.

- The container shall be labelled as containing human tissue, the name and address of the shipping facility and the name and address of the intended receiving facility.

- Containers shall comply with additional labelling requirements established by common carriers or by Inter-governmental, National, Regional and Local Law or Regulation.

B 2.6 00 Retrieval Documentation

Appropriate records of each donation procedure and all tissues retrieved shall be available and kept by the Tissue Bank.

All retrieved tissue shall be provided with an accompanying retrieval form including, at a minimum:

- the donor identity

- the date, time and place of the procedure
- the identity of the person (s) performing the retrieval
- the tissue(s) retrieved
- donor and tissue selection information

B 3.0 00 Tissue Banking General ***Procedures***

B 3.1 00 General

B 3.1 10 Written Procedures

The specific methods employed for processing may vary with each type of tissue and with the manner in which it has been retrieved. Each type of tissue shall be prepared according to a written procedure, which shall conform with these Standards and other applicable Standards, resulting in processed tissues appropriate for safe and efficient clinical use.

B 3.1 20 Process Validation

All steps involved during the processing of tissues shall be validated, when appropriate, to demonstrate the effectiveness of procedures.

When computers are used as part of a processing or ***Quality Management System***, the computer software shall be validated.

When validation cannot be adequately evidenced through testing, validation shall be evidenced through documentation demonstrating adequate design, development, verification and maintenance procedures.

B 3.1 30 Quality Controls

Tests and procedures shall be performed to measure, assay or monitor processing, preservation and storage methods, equipments and reagents to ensure compliance with established tolerance limits. Results of all such tests or procedures shall be recorded.

B 3.1 40 Records Management

Appropriate records of each tissue processed shall be kept by the Tissue Bank.

Records shall allow traceability of tissues, including the different steps in the preparation, the date and time of the procedure, the identity of the person performing the ***procedure and*** the record of the materials used.

Laboratory results (e.g. microbiology/processing cultures) and other test results used to determine final release shall be ***archived by*** the Tissue Bank distributing the tissue.

B 3.2 00 Unique Tissue Identification Number

Each individual tissue shall be marked with a unique identification number to relate each specimen to the individual donor.

B 3.3 00 Reagents, Container ***and*** Packaging

B 3.3 10 Reagents

The reagents used in preservation and processing shall be of appropriate grade for the intended use, be sterile, if applicable, and conform to existing Regulation. The origin, characteristics and expiration date of reagents shall be monitored and recorded.

B 3.3 20 Tissue Container

The type of tissue container may vary with the type of tissue and processing. They shall maintain the tissue sterility and integrity, withstand the sterilisation and storage methods utilised and avoid the production of toxic residues. They shall conform to applicable Inter-governmental, National, Regional and Local Law or Regulation.

Each tissue container shall be examined visually for damage or evidence of contamination before and after processing and prior to its dispatch.

B 3.3 30 Tissue Outer Package

Packaging shall ensure integrity and effectively prevent contamination of the contents of the final container. It shall conform to applicable Transportation Regulation.

B 3.4 00 Pooling

Tissue from each donor shall be processed and packaged in such a way as to prevent contact and cross-contamination with tissues from other donors.

If tissues are subsequently treated in batches (e.g. sterilisation), a unique batch number shall be assigned and added to the records of the tissues.

Pooling of donors is not recommended and should only be accepted for specific tissues. The size of the pool should be limited to the minimum number of donors and traceability to each donor has to be ensured. ***If pooling is used for specific tissues, a fully documented rationale and risk assessment shall be undertaken to document safety.***

B 3.5 00 Environmental Control

Processing steps shall take place in an appropriately controlled environment.

Tissue processing in an ***Open System*** shall have the environmental conditions and monitoring of the area clearly defined (such as for a “clean room” or laminar flow cabinet).

Records shall be maintained to demonstrate that the area is monitored for microbiological contamination and air control.

B 3.6 00 Storage Conditions

B 3.6 10 Temperature

Acceptable temperature ranges for storage shall be established.

Temperature monitoring of storage:

Low temperature (refrigerated or frozen) storage devices and ***incubators*** shall be connected to a central alarm system or each shall be equipped with an audible alarm system, that will sound when the temperature deviates from the acceptable storage range.

The alarm system shall be connected to an emergency power source. Continuous recording and daily review of data are recommended.

B 3.6 20 Storage of Quarantined or Unprocessed Tissue

There shall be a system of Quarantine for all tissues to ensure that they cannot be released for clinical use until they have met the defined acceptable criteria for release.

Storage areas of quarantined or unprocessed tissue shall be separate from storage areas of tissue approved for processing or ready for distribution. The

storage areas shall be clearly labelled as containing quarantined, released for processing or processed finished tissue.

B 3.7 00 Documentation Reviewing and Tissue Inspection

B 3.7 10 Incoming Inspection

Staff shall inspect the tissue container upon arrival from the procurement facility in order to ensure the integrity of the container(s), the presence of proper identification and documentation.

B 3.7 20 Review of Donor Eligibility

The donor's medical history, the physical examination, the results of tissue procurement microbiologic tests and donor blood testing, and if performed, the results of an autopsy, shall be reviewed by the Medical Director or designee.

Quarantined tissues shall be reviewed prior to distribution after all testing has been satisfactorily completed.

B 3.7 30 Sizing of Specimens

Specimen sizing may be made by actual measurements or by imaging sizing techniques.

B 3.7 40 Inspection Prior to Release Into Finished Inventory

Prior to the release of tissue into the Finished Inventory, a final review shall be made of donor suitability, procurement, ***production, processing records***, Quality Control ***tests, the*** finished tissue, containers, closures and labels shall be inspected and approved by the Medical Director or designee.

B 3.7 50 Final Inspection

Prior to distribution, final inspection of ***the*** container, label and documentation shall be performed to ensure accuracy and integrity.

B 3.8 00 Non-Conforming Tissues

Tissues failing any portion of the review process shall be maintained in quarantine pending disposal and shall not be released for clinical use.

There shall be a documented policy for discard of tissue unsuitable for clinical use.

B 3.9 00 Expiry Dates

Expiry dates shall be established for all tissue released from a Tissue Bank. If the dating period is 72 hours or less, the hour of expiration shall be indicated on the label. Otherwise, the dating period ends at midnight of the expiration date.

B 4.0 00 Specific Processing Procedures

B 4.1 00 General

Section A relating to written procedures, process validation, quality control and record management always apply.

All tissues rejected due to the ineligibility of the donor cannot be used for transplantation, even after processing including sterilisation or disinfection.

Even if terminal sterilisation or disinfection using physical or chemical ***agents are*** used, the procurement and processing shall be ***adequate to minimise*** the microbial content of tissues to enable the subsequent sterilisation-disinfection process to be effective.

Appropriate indicators for sterilisation must be included in each sterilisation batch.

B 4.2 00 Disinfectant or Antibiotic Immersion

If disinfectants or antibiotics are used after retrieval, the tissues shall be immersed in a disinfectant or in ***an*** antibiotic solution following sterility testing and before final packaging. The type of solution used shall be specified on documentation.

B 4.3 00 Fresh Tissue

Fresh allografts (e.g. small ***fragments of*** articular ***cartilage and skin***) are aseptically procured in an operating room.

Fresh Tissue is usually stored refrigerated at 4°C ***or in accordance with written procedures***.

Fresh Tissue shall not be used in a patient until donor blood testing is completed according to these Standards, available bacteriologic results are acceptable and donor suitability has been approved by the Medical Director or designee.

B 4.4 00 Frozen Tissue

After aseptic procurement in ***the*** operating room, frozen tissue are placed in a -40°C or colder controlled environment within 24 hours of procurement. Subsequent manipulation of tissues (e.g. cleaning ***and*** cutting) shall be undertaken aseptically.

B 4.5 00 Cryopreserved Tissue

A cryopreservative solution (e.g. DMSO or Glycerol) is usually added to treat the tissue prior to freezing. Documentation of the concentration of ***cryoprotectants and nutrients*** or isotonic solutions in the cryopreservative solution shall be maintained.

Properly packaged specimens are frozen by placing the specimens below -40°C, or may be subjected to control rate freezing using a computer assisted liquid nitrogen freezing device.

If a programmed control-rate freezing method is employed, a record of the freezing profile shall be evaluated, approved and recorded.

B 4.6 00 Freeze-Dried Tissue

B 4.6 10 Freeze-Drying Methods

Various Protocols of freeze-drying tissues exist. Freeze-drying is a method for preservation, but is not a sterilisation method; sterility shall be assumed by Aseptic Protocol or additional sterilisation.

After a standardised procedure for freeze-drying has been developed, a Quality Control Programme for monitoring the performance of the freeze-dryer shall be documented.

Freeze-dried tissues shall be stored at room temperature or colder.

B 4.6 20 Freeze-Drying Controls

Each freeze-drying cycle must be clearly documented, including length, temperature and vacuum pressure at each step of the cycle.

Representative samples shall be tested for residual water content.

B 4.7 00 Simply Dehydrated Tissue

B 4.7 10 Dehydration Method

The use of simple dehydration (evaporation) of tissues as a means of preservation shall be controlled in a manner similar ***of freeze-drying***. Temperatures of simple dehydration shall be below 60°C

B 4.7 20 Dehydration Controls

Each dehydration cycle shall be monitored during operation for temperature.

Following dehydration, representative samples shall be tested for residual moisture.

B 4.8 00 Irradiated Tissue

B 4.8 10 Irradiation Methods

Commercial or hospital radiation facilities are available for ionising irradiation.

The ***minimum recommended*** dose for bacterial decontamination is 15 ***kGy (kiloGray)***.

The minimum recommended dose for bacterial sterilisation is 25 ***kGy(kiloGray)***.

Viral inactivation would require higher doses and depends on numerous factors. For this reason no specific dose can be recommended, but shall be validated, when applicable.

The used Protocol shall be validated taking in account the initial bioburden, and shall be performed by facilities

following **Good Irradiation Practices** ***(see IAEA Code of Practice for the Radiation Sterilization of Biological Tissues)***.

B 4.8 20 Irradiation Sterilisation Controls

Sterilisation by ionising radiation shall be documented. The processing records include the name of the facility and the resultant dosimetry for each batch.

B 4.9 00 Ethylene Oxide Sterilised Tissue

B 4.9 10 Ethylene Oxide Sterilisation Method

Care should be taken when using ethylene oxide since the residues may have toxic effects already demonstrated for musculo-skeletal allografts in the literature.

Following appropriate processing procedures, the tissues are placed in ethylene oxide permeable containers and exposed to the ethylene oxide gas mixture following the manufacturer's suggested Guidelines. The conditions of exposure may need to be individualised depending upon the nature of the specimens to be sterilised.

A Quality Control Programme shall demonstrate that equipment meets requirements in temperature, humidity and gas concentration for the selected period.

Following ethylene oxide sterilisation, an appropriate aeration procedure shall be followed, to allow removal of residual ethylene oxide and/or its breakdown products (**Ethylene Chlorhydrin and Ethylene Glycol).**

B 4.9 20 Ethylene Oxide Sterilisation Controls

Chemical indicator strips shall be included in each batch. A validated procedure shall be run with each lot of tissue to document that sterilisation has been achieved.

Monitoring for residual levels of chemicals or their breakdown products shall be conducted from representative samples of the finished tissues of each batch.

B 4.10 00 Other Processing Methods

B 4.10 10 Other Inactivation Methods

Some chemical agents only have a decontamination ***role. Other*** agents may have an inactivation effect on

specific pathogens. The efficiency of these agents towards the treated type of tissue shall be validated.

The use of chemical and possible presence of trace residuals shall be included in the information accompanying the tissue.

Under specific conditions, heat may be used to decontaminate or sterilise some type of tissues. The used Protocol shall be validated taking in account the initial bioburden and shall be performed by a recognised facility.

B 4.10 20 Bone Demineralisation

Several methods and procedures for the formation of demineralised bone are available and acceptable.

Controlled quality reagents shall be used.

Residual calcium obtained by the method shall be determined

B 5.0 00 Labelling

B 5.1 00 General Requirements

B 5.1 10 Rationale

There shall be written procedures designed and followed to ensure that correct labels and labelling are used for tissue identification.

B 5.1 20 Nomenclature

Standard measurement nomenclature shall be used to describe tissues and the processing they have undergone.

B 5.1 30 ***Label Integrity***

The tissue label applied by the Tissue Bank facility shall not be removed, altered or obscured.

B 5.1 40 Visual Inspection

When visual inspection through the container is possible, a sufficient area of the container shall remain uncovered to permit inspection of the contents.

B 5.2 00 Tissue Containers Labelling

Tissue containers shall be labelled so as to identify, as a minimum:

- ***The human nature of the contents***
- ***Product description***
- Name and address of Tissue Bank
- Tissue identification number
- Expiration date

The following information shall be included on the label, if possible, otherwise on the accompanying documentation:

- Amount of tissue in the container expressed as volume, weight or dimensions or such combination of the foregoing as needed, for an accurate description of the contents.

- Sterilisation or inactivation procedure used, if applicable.

- Batch number, if applicable

- Potential residuals of added preserving ***and*** processing agents/solution (e.g. antibiotics, ETOH, ETO, DMSO).

- Recommended storage conditions

B 5.3 00 Package Insert

B 5.3 10 General

All tissues shall be accompanied by a document describing the nature of tissue and processing methods and instructions for proper storage and reconstitution, when appropriate. Specific instructions shall be enclosed with tissue, which require special handling.

B 5.3 20 Accompanying Documentation Requirements

Accompanying documentation shall contain all the information described for container labelling and the following additional information:

- Origin of tissue (country of procurement)
- The nature and results of biological tests performed on the donor using appropriate and licensed tests.
- Processing methods used and results of sterility tests or inactivation controls.
- Special instructions indicated by the particular tissue for storage or implantation. Tissue that is to be reconstituted at or prior to the time of use shall include information on the conditions, under which such tissue shall be stored and reconstituted prior to implantation.
- Indications and contraindications for use of tissue, when necessary.
- Statement ***that each*** tissue shall be used for a single patient only.

B 5.4 00 Tissue Outer Package Labelling

Labelling of the tissue outer package shall conform to Transportation Regulations, when applicable.

B 6.0 00 Distribution

B 6.1 00 General

Tissues can be distributed for a specific patient to a physician, dentist and other qualified medical professional or to a storage facility located in another institution for local use or distributed to another Tissue Bank.

Distribution for therapeutic use shall be based on medical criteria on equitable bases, in accordance with Inter-governmental, National, Regional and Local Law or Regulation and practice.

There shall be written procedures and documentation for all tissues distributed

The clinical team using the tissue shall have instructions for contacting the Tissue Bank for any question they have and shall be made aware of the following:

- ***Action to be taken in the event of loss of integrity of the package***
- ***Action for reporting of adverse event***
- ***Action for the return or the disposal of unsuitable or unused tissue.***

B 6.2 00 Traceability

There shall be an effective system that enables the traceability of tissues between the donor, the processed tissue and the recipient.

It is the responsibility of the hospital tissue storage and distribution facility or clinician to ***implement*** recipient ***records and*** to inform the Tissue Bank of the destination of tissues (implantation date, surgeon ***and*** recipient identification).

Tissue Banks shall maintain records which document the destination of distributed tissue: implantation (date, surgeon ***and*** recipient identification), destruction (date and place) ***and of any adverse event reports***.

B 6.3 00 Transportation

Maintenance of (upper and/or lower parameters) environmental conditions during transit, as defined in the written procedure of the Tissue Bank, shall be ensured.

Use of hazardous elements such as dry ice or liquid nitrogen shall comply with relevant Regulations.

B 6.4 00 Accompanying Documentation

The release of tissue from storage shall include all documentation originating from the Tissue Bank. Surgeons shall be aware that copies of this documentation shall be maintained in the recipient's medical records.

B 6.5 00 Return into Inventory

Issued tissues shall not be returned to the Tissue Bank without prior ***consultations with*** the Medical Director or designee. Tissue must be in its original unopened container

and the storage conditions must have been maintained as required.

B 6.6 00 ***Adverse Events***

Reports of adverse events shall be evaluated by the institution where the tissue was used and reported immediately to the Tissue Bank.

All adverse events shall be reviewed by the Medical Director and appropriate action documented, in accordance with Inter-governmental, National, Regional and Local Law or Regulation. Identified transmission of disease shall be reported to the Public Health Authorities, processing Institutions, to the donor's personal ***physician, if clinically relevant*** and to physicians involved in implantation of the ***tissue, in accordance with Inter-governmental, National, Regional and Local Law or Regulation on Confidentiality***.

When donor to recipient disease transmission through tissue use is discovered, all facilities involved in the procurement and distribution of ***organs or tissues*** from the infected donor shall be notified without delay.

Written reports of the investigation of adverse events, including conclusions, follow up and corrective actions, shall be prepared and maintained by the Tissue Bank in an adverse ***event*** file.

B 6.7 00 Recall

A written procedure shall exist for recall of tissues.

B 6.8 00 Distribution to Storage Facilities Outside the Tissue Bank ***(Depot).***

B 6.8 10 General

When a storage facility is located outside the Tissue Bank, the institution where this facility is located is responsible for establishing acceptable storage and record keeping procedures to ensure the maintenance of the safety and efficacy of tissue from receipt to use and the traceability of tissue and recipients.

The relevant part of these Standards shall be made available to these institutions. ***These storage facilities (Depot) shall be subjected to Quality Audit and Control from the Tissue Bank***.

B 6.8 20 Labelling

Labels on ***tissue containers*** shall not be altered, made invisible or removed.

B 6.8 30 Storage

Tissue storage shall conform with Guidelines established by the distributing Tissue Bank.

B 6.8 40 Records

Records shall document, as a minimum, the receival date of tissue and the destination (transplant date, the recipient's identity and transplant surgeon). These destination records shall be transmitted to the Tissue Bank.

B 6.9 00 Distribution to Another Tissue Bank

The associated Tissue Bank should adhere ***to these*** Standards.

B 6.10 00 Acquisition of Tissue from Another Tissue Bank

B 6.10 10 Medical Director Approval

Prior to acquiring tissue from another Tissue Bank, the Medical Director shall ensure that the Tissue Bank works according to these Standards or according to comparable recognised Standards.

B 6.10 20 Labelling

Labels on processed tissue acquired from another Tissue Bank shall not be altered, made invisible or removed.

B 6.10 30 Distribution Record

Accompanying documentation from the original Tissue Bank shall be forwarded with the tissue to the clinical team. After implantation, the destination record (transplant date, the recipient's identity and

transplant surgeon) shall be forwarded to the original Tissue Bank.

ANNEXES

Annex 1: Glossary

ADVERSE EVENTS [Synonym ADVERSE OUTCOME/REACTION]: An undesirable effect or untoward complication in a recipient consequent to or reasonably related ***to tissue*** transplantation.

ALLOGRAFT: A graft transplanted between ***two different*** individuals of the same species.

ASEPTIC RETRIEVAL: The retrieval of tissue using methods that restrict or minimise contamination with microorganisms from the donor, environment, retrieval personnel and/or equipment.

BRAIN DEATH/BRAIN STEM DEATH: Complete and irreversible cessation of brain stem and brain ***encephalic*** functions and certified according to National Laws. Synonym = death.

CLEAN ROOM: A room in which the concentration of airborne particles is monitored and controlled to defined specification limits.

COMPLIANCE: Conforming to established Standards or Regulations.

CONTAINER: ***An enclosure for one unit of transplantable tissue***.

CONTROLLED ENVIRONMENT: An environment, which is controlled with respect to particulate contamination, both viable and non-viable particles, is controlled. May also include temperature and humidity controls

CORONER: (See Medical Examiner)

CORRECTIVE ACTION: Steps taken to ameliorate non-compliance.

COST: The actual costs for retrieval, processing, preservation, storage, distribution, education, research and development

CROSS-CONTAMINATION: The transfer of infectious agents ***from tissues to other tissue*** or from one donor's tissue to another donor's tissue.

DEATH: (See Brain Death)

DISINFECTION: A process that reduces the number of viable cellular microorganisms, but does not necessarily destroy all microbial forms, such as spores and viruses.

DISTRIBUTION: Transportation and delivery of tissues for storage or use in recipients.

DONOR MEDICAL HISTORY INTERVIEW: A documented dialogue with an individual or individuals who would be knowledgeable of the donor's relevant medical history and social behaviour; such as the donor, if living, ***the next of kin***, the nearest available relative, a member of the donor's household, other individual with an affinity relationship and/or the primary treating physician. The relevant social history includes questions to elicit whether or not the donor met certain descriptions or engaged in certain activities or behaviours considered to place such an individual at increased risk for HIV and Hepatitis or other diseases.

DONOR REGISTRY: A formal compilation of individual's intent relating to donation that may be maintained by a Governmental agency or private establishment.

DONOR SELECTION/DONOR SCREENING: The evaluation of information about a potential donor to determine whether the donor meets qualifications specified in the SOPs and Standards. This includes but is not limited to, medical social and sexual histories, physical ***examination and*** laboratory test results (and autopsy findings, if performed).

DONOR: A living or deceased individual who is the source ***of tissue*** for transplantation in accordance with established medical criteria and procedures.

END-USER: A healthcare practitioner who performs transplantation procedures.

FACILITY: Any area used in the procurement, processing, sterilisation, testing, storage or distribution of tissue and tissue components.

FINISHED INVENTORY: Storage of finished tissue

FINISHED TISSUE: Tissue that has undergone all of the stages of processing, ***packaging and is approved for distribution***.

GIFT DOCUMENT: A legally recognised document in which an individual indicates his/her wishes as they relate to donation of organs ***and*** tissues.

GOOD ***TISSUE BANKING*** PRACTICES: Practices that meet accepted Standards as defined by relevant Government or professional organisations.

HPC: Haematopoietic Progenitor Cells
INSPECTION: An examination of a Tissue Bank to ascertain Good ***Tissue banking*** Practices.

INSPECTION: An examination of a Tissue Bank to ascertain Good Tissue Banking Practices

LABELING MATERIAL: Any printed or written material including labels, advertising, and/or containing information (for example package insert, brochures, pamphlets) related to the tissues.

LABELING: Includes steps taken to identify the material and to attach the appropriate labels on the container or package so that it is clearly visible. Includes the package insert which is the written material accompanying a tissue graft bearing information about the tissue, directions for use and any applicable warnings.

MEDICAL EXAMINER [Synonym Coroner]: Governmental official (usually a pathologist) charged with investigating deaths and determining cause of death.

NATIONAL REGULATORY AUTHORITY [NRA]: A body appointed by the Government with the goal of controlling Tissue Banking practices.

NEXT OF KIN: The person(s) most closely related to a deceased individual as designated by applicable law.

NON-COMPLIANCE: Non-conformance to established standards or regulations.

OPEN ***SYSTEM***: A system which has been breached but where every effort is made to maintain sterility by the use of sterile material and aseptic handling techniques in a clean environment.
ORGAN (See Vascular Organ).

PACKAGING (See Container)

PROCESSING: ***Any activity performed on tissue, other than tissue recovery, including preparation, preservation for storage and/or removal from storage, to assure the quality and/or sterility of human tissues***.

QUALITY: Totality of characteristics of a product, process or system that bear on its ability to satisfy customers or other interested parties.

QUALITY ASSURANCE (part of Quality Management): Planned and systematic actions necessary to provide confidence in fulfilling ***Quality Requirements*** (See Quality Requirements)

QUALITY AUDIT: A documented review of procedures, records, personnel functions, equipment, materials, facilities, and/or vendors in order to evaluate adherence to the written SOPs, Standards, or government laws and regulations.

QUALITY CONTROL (part of Quality Management): Operational techniques and activities that are used to fulfil Requirements for Quality.

QUALITY MANAGEMENT: ***All activities of the overall management function that determine the Quality Policy, Objectives and Responsibilities, and their implementation by means of Quality Planning, Quality Control, Quality Assurance and Quality Improvement, within the Quality System***.

QUALITY REQUIREMENTS: Requirements for the characteristics of a product, a process or a system.

QUALITY MANGEMENT SYSTEM (See Quality Management).

QUARANTINE: The status of retrieved tissue or packaging material, or tissue isolated physically or by other effective means, whilst awaiting a decision on their release or rejection.

RECALL: The requested return of finished tissue known or suspected to be non-compliant to the Tissue Bank, in accordance with the instructions contained in an advisory notice.

RECIPIENT: An individual into whom organs, ***tissue*** is transplanted.

RETRIEVAL [synonyms Recovery, Procurement, Removal, Harvest]: The removal of ***tissues*** from a donor for the purpose of transplantation.

SAFETY: A Quality ***of tissue*** indicating handling according to standards and substantial from the potential for harmful effects from recipients.

STANDARD OPERATING PROCEDURES [SOPs]: A group of Standard Operating Procedures detailing the specific policies of a Tissue Bank and the procedures used by the staff/personnel. This includes, but is not limited to procedures to: assess donor suitability and retrieve, process, sterilise, quarantine, release to inventory, label, store, distribute and ***recall tissue***.

STERILISATION: A validated process to destroy, inactivates, or reduces micro-organisms to a sterility assurance level of 10^{-6}.

STERILITY ASSURANCE LEVEL: The probability of detecting an unsterile product, ***tissue***.

STORAGE: Maintenance of tissues in a state ready for distribution.

TERMINAL STERILISATION: Sterilisation that takes place at the end of processing the tissue, in the final packaging

TISSUE: Human tissue includes all constituted parts of a human body, including surgical residues and amnion, but excluding organs, blood and blood products, as well as reproductive tissues such as sperm, eggs and embryos. New products engineered from human tissue are included. ***The word "Tissue" in this text applies to all types of tissues, including corneas and to cells***.

TISSUE BANK: An entity that provides or engages in one or more services involving ***tissue*** from living or cadaveric individuals for transplantation purposes. These services include assessing donor suitability, ***tissue*** recovery, ***tissue*** processing, sterilisation, storage, labelling and distribution.

TRACEABILITY: The ability to locate ***tissue*** during any step of its donation, collection, processing, testing, storage and distribution. It implies the capacity to identify the donor and the medical facility receiving the cells and/or tissue or the recipient.

TRANSPLANTATION: The removal of tissues and/or cells and grafting of these ***tissues*** whether immediately or after a period of preservation and/or storage. Transplantation may be from one person to another (allogeneic) or from a person to themselves (autologous).

VALIDATION: Refers to establishing documented evidence that provides a high degree of assurance that a specific process 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.

VASCULAR ORGANS: Any part of a human body consisting of vascularised, structured arrangement of cells, which removed, cannot be replicated by the body. Example: Heart, liver, lung, kidney, pancreas, intestine.

Annex 2: G*uidelines of Factors to be Considered for Determining Risk* for Human Immunodeficiency Virus or B or C Hepatitis

- Men who have had sex with another man in the preceding 12 months.

- Persons who report non-medical intravenous, intramuscular or subcutaneous injection of drugs in the preceding 12 months.

- Men and women who have engaged in sex in exchange for money or drugs in the preceding 12 months.

- ***Persons with a history of chronic Hemodialysis***

- ***Persons with a history of Haemophilia or related clotting disorders who have received human-derived clotting factor concentrates.***

- Persons who were sexual partners of persons having a HIV or B or C Hepatitis history, manifestations, or risk factors previously described, in the past 12 months.

- Percutaneous exposure or contact with an open wound, non-intact skin or mucous membrane to blood thought to be at high risk for carrying HIV or Hepatitis in the preceding 12 months.

- Inmates of correctional systems in past 12 months.

- Diagnosed or treated for Syphilis or Gonorrhea in past 12 months.

- A potential tissue donor who has received a blood transfusion within 12 months prior to death may only be accepted as a tissue donor after individual approval from the Medical Director.

- The donor is not eligible if in a deferral status of any Blood Services Donor Deferral Register. The local blood centre(s) shall be checked each time possible (blood donor card available).

- Tattoo, ear piercing, body piercing, and/or acupuncture, unless by sterile, non-reused needle or equipment, in the preceding 12 months.

Annex 3 Primary Tumours of the Central Nervous System: Evaluation of a Suitable *Donor. A Reference List*

No Contraindication

Pituitary Adenoma
Pinelcytoma
Hemangioblastoma
Schwannoma
Choroid Plexus Papilloma
Ependimoma
Oligodendroglioma differentiated
Craniopharyngioma
Benign Meningioma
Pilocytic astrocytoma
Epidermoid tumours

Contraindication

Medulloblastoma
Chordoma
Glioblastoma multiforme
Highly anaplastic Oligodendroglioma
Anaplastic Epidimoma
Anaplastic Meningioma
Primary CNS Lymphoma
Pineoblastoma
CNS Sarcomas
Astrocytoma grade II
Astrocytoma grade III

Annex 4: Example of Algorithm for Calculating the Hemodilution of a Donor Having Received Blood, Blood Components, or Plasma Volume Expanders Within 48 Hours Prior to Death

The following equation allows calculation of a potential donor 50% plasma volume:

50% plasma volume (ml) = 21 * donor's body weight (kg)

The equation as been calculated as follows:

Total blood volume per kg = 1kg * 70 ml = 70 ml

Total plasma volume per kg

= 70 ml (Total blood volume per kg) * 1,0 -0,40 (normal adult hematocrit)

= 70 ml * 0,60 = 42 ml

50% plasma volume per kg = 42 ml (total plasma volume per kg) * 0,50 = 21 ml per kg

Annex 5: References and Contact Addresses

REFERENCES

- American Association of Tissue Banks (AATB)
  - Standards for Tissue Banking (1984, 1985, 1987, 1989, 1993, 1996, 1998, 2001)

- Australian Code of Good Manufacturing Practice- Human Blood and Tissues. Therapeutic Goods Administration, 2000.

- Council of Europe
  - Guide on Safety and Quality Assurance for Organs, Tissues and Cells (Version 11. CDSP, Released for Consultation 1/2001)

- European Association of Tissue Banks (EATB)
  - EATB General Standards for Tissue Banking (1995)
  - EATB and EAMST Standards for Musculo-skeletal Tissue Banking (1997, revised1999)
  - EATB Standards for Skin Banking and Banking of Skin Substitutes (1997)

- ***IAEA Code of Practice for the Radiation Sterilization of Biological Tissues. (IAEA Vienna)***

- Radiation and Tissue Banking. Ed by G.O. Phillips. World Scientific. Singapore, New Jersey, London, Hong Kong. 200

- UK Code Of Practice for Tissue Banks. Department of Health. United Kingdom. 2001

CONTACT ADDRESSES:

- American Association of Tissue Banks (AATB)
  1350 Beverly Road, Suite 220A, McLean, VA 22101, USA
  www.aatb.org
- Asia-Pacific Surgical Tissue Banking Association
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- Council of Europe
  Karl Friedrich Bopp, Health Department, Council of Europe, 67075 Strasbourg Cedex, France
  www.coe.int
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  www.eatb.de

- Latin American Association of Tissue Banking

Part 2: GUIDE FOR LEGAL AND REGULATORY CONTROL

INTRODUCTION

This Section is intended to assist Governmental Control Authorities (GCA) and Tissue Banks in their joint task of improving the quality of ***human*** tissues for transplantation through Regulation and Legislation that interface with Standards.

Each member of the IAEA and their Regulatory/Legislative bodies must necessarily determine the appropriate path for such Regulation/Law to follow, based on the technical capabilities of their region, religious beliefs and practices and healthcare systems. Within these key topics, many options are available for consideration.

HISTORICAL PROGRESSION

The first Tissue Banks were started in the 1950's, primarily in response to needs for bone, corneas and skin. Through the 1960's and 1970's, Tissue Banks began to proliferate, although they were usually small programmes that primarily served the hospital at which the Tissue Bank was located. Laws relating to organ and tissue donation, declaration of death and ***donor consent*** were passed in many countries in the 1970's through the 1980's.

Starting in the mid-1980's, Standards for Tissue Banking were developed, and often were accompanied by accreditation programmes organised by Tissue Banking Associations. Even in countries with well-established Tissue Banks, the development and enforcement of Regulations and Laws did not occur until the 1990's, when concerns regarding safety of donated tissues increased.

In the new century, Tissue Banking Regulations and Laws in developing countries have been passed, as have expanded Laws in other countries with well-developed tissue donation systems.

LAWS AND REGULATIONS

Laws and Regulations concerning a wide range of topics are necessary, including:

1- Donation/Transplantation/Recovery/Waiting Lists
2- Consent
3- Organisation of the Tissue Bank
4- Interrelationships with Organ Donation Programmes
5-. Registration/Licensing/Accreditation/Authorisation of the Tissue Bank

6- Import/Export of Tissue
7- Financial Aspects of Tissue Banking
8- Enforcement and Compliance

1-Donation/Transplantation/Recovery/Waiting Lists

a) A Law defining death (including Brain Stem Death or Brain Death) is mandatory in order for cadaveric donation of vascular organs ***and tissues***. Because tissues may also be retrieved from a brain dead organ donor, the Standards should reference Brain Death Laws, ***if the Tissue Bank is*** prepared to accept tissues from donors meeting Brain Death criteria.

   Ideally, this Law will also address how death must be declared, and by whom (e.g., brain death may be determined by a registered medical practitioner not involved with the recovery or transplantation of organs/tissues and using clinical criteria).

b) A Law or Regulation covering the mechanisms for organ and tissue donation is mandatory.

These Laws must outline how an individual may ***become or refuse to be a donor, the definition of organs and tissues that may be donated, the existence of a Referral System, to whom and how organs and tissues may be donated (allocation rules) and allow compensation for donation-related expenses***.

c) Regulations that address at a minimum the donation, recovery, processing, storage and distribution of tissues are key to insuring the safety of the recipient.

These Regulations must include a list of tissue that are applicable to the Regulations, Guidelines or Rules for donor screening criteria, donor approval systems, documentation, systems to guard against cross-contamination of tissue, labelling, quality systems, processing, validation of systems, storage, distribution and traceability of tissues.

These Regulations should also be based upon Standards established for/by the Tissue Bank.

d) Regulations regarding the donation of tissue from living donors (including amnion and surgical residues) are necessary and should be based upon the Tissue Banking Standards.

2- Consent

a) Laws addressing consent for donation are generally in place throughout the world, and vary widely, not only in content but also in practice.

At a minimum, a Consent Law must include who may donate (e.g., the individual prior to his/her death, the individual's next of kin following death, or a patient prior to the donation of living tissues, etc.), whether the consent is presumed or informed ("opting out" or "opting in") and whether the individual's wishes may be countermanded by his/her ***next of kin***.

In addition, a mechanism for an individual to change his/her mind about donation prior to death must be included as part of the Law/Regulation.

Finally, Laws covering donor registries may also be considered as a way of insuring an individual's choice is carried out, and as a way to increase donation rates in the region.

b) Presumed Consent:

Many countries have adopted Presumed Consent Laws, in which an individual is assumed to be a donor unless he/she has specifically indicated his/her wish not to be a donor. This decision may be made officially through a non-donor registry (e.g., Belgium, France, Portugal) or informally (e.g., family discussion). This system is also known as "opting out". The Presumed Consent Laws in several countries imply the family confirmation of Presumed Consent.

Despite the fact that Presumed Consent Laws are in place in many countries, few tissue, eye or organ recovery agencies will proceed with the retrieval process without first discussing donation with the patient's family. They either obtain the ***next of kin's*** informed consent for donation or verify the patient's desire to be a donor. In other countries, ***however, consent confirmation*** for tissue donation may not be routinely obtained from family members.

In some countries, the Medical Examiner/Coroner may allow the recovery of corneas and other tissues without family consent. However, this practice is under increasing scrutiny, due to the need for a family interview in order to

determine medical suitability of the donor, and due to the perception that it may violate a donor family's rights.

c) Informed Consent

Informed Consent generally involves a discussion with the family of a recently deceased person regarding his/her desire or intent to be a donor, or in the absence of such knowledge or executed gift document, the family's desire to donate organs, eyes or other tissues for transplantation or research.

In general, the consent conversation provides the potential donor family information about the recovery process and the uses of tissue for transplantation or research, what a "reasonable person" would want to know in order to make an informed decision.

d) ***Living Donor Consent***

Regulations for the donation of tissues from living donors should require, as a minimum, that Informed Consent be obtained from the donor or his/her legal guardian if he/she is not of majority age.

Surgical residue collection (eg. femoral head, skin and amnion) implies information and consent from the patient before collection.

3-.Organisation of the Tissue *Banks*

Regulations addressing the organisation of the Tissue Bank should reference ***International Standards for Tissue Banks*** and may include:

- Personnel
- Training
- Building Design & Facilities
- ***Quality Management***
- Equipment Requirements

4-.Interrelationships with Organ Donation Programmes

a) ***Collaboration between Tissue Banks and Organ*** Donation/Transplantation Programmes is necessary to minimise confusion within the general public ***and donor*** hospitals.

It may be advisable to include ***language in Laws or Regulations that encourages such collaboration.***

Collaboration between recovery agencies can benefit all. It eliminates duplication of efforts (personnel, organisation, donor promotion/enlightenment programmes), minimises unnecessary expenditures and maximises recovery of ***organs and tissues*** when consent ***for all types*** are obtained at once.

In addition, it reduces the possibility that a bereaved family will be approached with multiple requests to donate

b) Because Laws exist regarding organ donation in many areas, Tissue Banking ***Laws and Regulations*** should be written so as to coincide with them wherever possible.

5-.Registration/Licensing/Accreditation/Authorisation

a) At a minimum, Regulations should provide some mechanism for Tissue Banks to be identified through Registration with the ***National Regulatory Authority (NRA) in order for the NRA*** to review the Tissue Banks' practices and to ***ensure*** compliance with established Regulations.

b) Licensing or official authorisation to operate may be preferred. Regulations requiring licensing must take into account the resources required (financial, personnel, technical) to perform in-depth inspections or evaluations of Tissue Banks.

If the ***NRA*** does not have the requisite resources, registration can be a reasonable alternative.

c) In some cases, the ***NRA*** is unable to adequately inspect or license Tissue Banks. It may, however, choose to contract such activities to another agency or private accrediting body, such as one that accredits laboratories, hospitals or ***Tissue Banks***.

6-.Import/Export of Tissue

a) With the global economy now extending into tissue donation and transplantation, it is critical for ***Laws and Regulations*** that address the import and export of donated human tissues. For instance, export of donated human tissues might be allowed only if all needs in the country have been met.

Or, export of tissues might be allowed outright, depending on the Laws and Regulations of the other country.

b) Import of tissue requires specific rules in order to protect tissue ***recipients and*** ***compliance with these Standards or equivalent Standards, including ethical aspects, donor consent and safety issues***.

7-.Financial Aspects of Tissue Banking

a) Tissue Banks may be funded in a variety of fashions, including: Governmental agency funding, private funding, funding through investors or through public or private hospitals or universities. ***Laws and Regulations*** outlining how Tissue Banks receive compensation or reimbursement for their costs, whether they may charge patients or hospitals for tissue are all necessary.

b) The required financial structure of a Tissue Bank should also be established (non-profit or for-profit or public).

c) Monetary payment or advantages for the donation may not be made to living donors, cadavers donor's next of kin or any donor-related party, excluding compensation for donation-related expenses.

However, there are some locations that are considering pilot Programmes that would allow for some moderate financial compensation or reimbursement for travel or funeral expenses to donor families.

d) ***Commercial sale of tissues is of ethical and safety concern***. ***However, many Laws allow for the cost recovering of all tissue transplantation operations, including research/development and educational costs***.

Several tissue processing technologies are covered by patent rights that should be respected. ***Sale of tissues*** is a very vague statement and regulatory and legislative bodies would be well advised to clearly define and regulate what is allowable and what is not acceptable.

8-.Enforcement/Compliance

a) ***Laws and Regulations*** must include enforcement and compliance of the Regulations, for without such enforcement the Regulations will be far less effective.

b) Enforcement and compliance should include inspections of Tissue Banks and systems for addressing non-compliance or violation of ***Laws and Regulations***. These could include requirements that the Tissue Bank destroy tissue, quarantine or retain tissue until corrective action is completed, notify hospitals, surgeons or patients of non-compliance, or issue a recall for all non-compliant tissue distributed. Penalties for non-compliance (e.g., closure of the Tissue Bank, financial penalties, civil and/or criminal prosecution) should also be considered and fully outlined.

c) Adverse Events/ Self-reporting of Non-compliance: The Regulations should include requirements that the Tissue Bank have a system for receiving reports of adverse events, and for addressing those reports. In addition, the Regulations should require that the Tissue Bank notify the ***NRA*** in the event of serious instances of non-compliance with Standards, SOPs and/or Regulations.

d) Internal Audits: The Regulations should include the requirement that the Tissue Bank perform periodic internal audits in order to assure compliance with Standards, SOPs and/or Regulations.

If multiple organisations or Tissue Banks are involved in the same **Tissue Banking process, the Regulations should address *which organisation* is ultimately responsible for the tissue. However, a Tissue Bank that engages another *organisation* or Tissue Bank under a contract, agreement or other arrangement, to perform any step in the process, should be responsible for ensuring that the work is performed in compliance with the requirements established in the *Laws and Regulations*.**

CONCLUSION

The development and implementation of appropriate ***Laws and Regulations*** is a complex, time-consuming and difficult undertaking. In order for such a system to become a functional reality, it is vital for Tissue Banks to enlist the support of key stakeholders such as end-users (surgeons, dentists, physicians, etc.), tissue recipients and tissue donor families. It may also be possible to enlist the support of the general public and charitable organisations that support programmes intended to better the well being of their fellow citizens.

The importance of donor families should be emphasised, as they can be a powerful advocate for donation, if they are respected and included in the process of improving donation and transplantation. If they are ignored, disrespected or marginalised, they can become an even more powerful group, raising ethical questions about the donation and transplantation system that can result in an overall decrease in donation rates.

The IAEA will encourage all Tissue Banks participating in the IAEA Radiation and Tissue Banking Programme to apply these Standards, in accordance with their national conditions, with the purpose of ensuring the safe clinical use of the tissues produced.