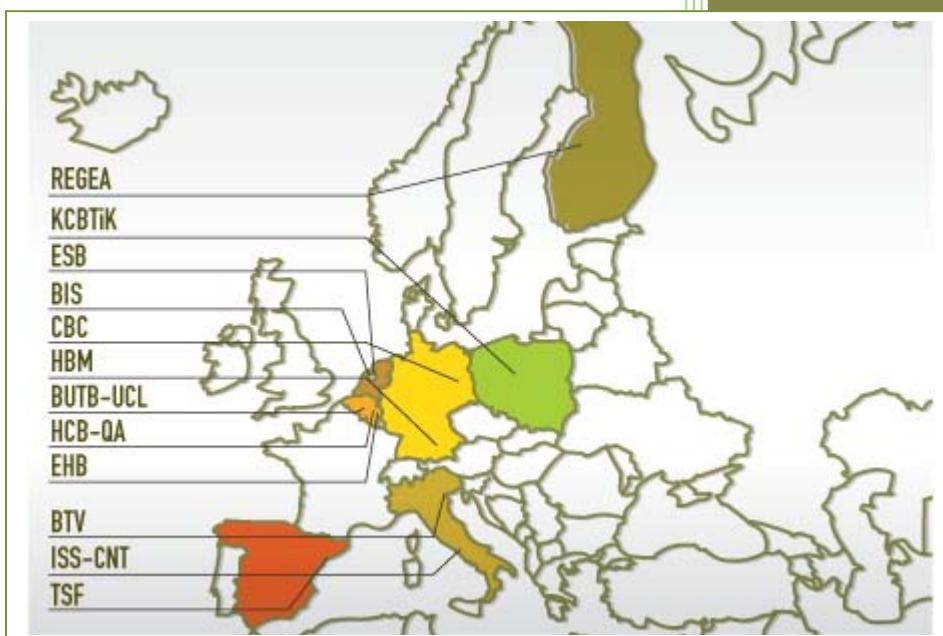


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PURPOSE AND SCOPE

The European Good Tissue Practice (GTP) guidelines and the adjacent training model have been established as an outcome of the EU-funded project - *Euro-GTPs* - to provide a *complete and detailed tissue banking information package* for tissue bankers as well as for tissue establishment (TE) inspectors in Europe. These guidelines bring together the current minimum regulatory requirements of the European tissue and cells Directives and go one step further - incorporating useful good manufacturing practice (GMP) principles and utilizing the expertise of tissue bank experts to provide a set of practical recommendations for good practice in European TEs. The GTPs are developed to be a helpful tool for all kinds of TEs in different phases of their development and evolution as well as for competent authorities (CA) when performing TE inspections.

The aim of the *Euro-GTP project* is to promote the application of these practices throughout Europe so as to increase the know-how and the level of performance of tissue banking staff, and to harmonize the techniques used. By harmonization of the practices to what is broadly considered as optimal, European TEs are expected to be able to routinely provide higher quality and safer tissues for transplantation and hence reduce the risk of disease transmission to recipients throughout Europe and increase the clinical effectiveness of transplanted grafts. This will contribute to a higher confidence in the exchange of tissues for transplant throughout Europe.

The GTP guidelines encompass procedural recommendations for (i) donor screening and selection for each tissue type, (ii) tissue procurement, processing, preservation and storage, as well as (iii) recommendations on how to validate these processes. The effectiveness of the recommended procedures has been assessed by putting them into practice in a TE with the required environmental conditions.

These guidelines have been structured in two main parts: **generic good tissue practices (GTPs)** and **tissue-specific GTPs**. The generic section comprises practical instructions on (i) generic processes carried out in TEs, (ii) risk assessment and (iii) validation methods for donor screening and tissue procurement, processing, preservation and storage, as well as basic requirements concerning infrastructure, personnel, documentation management, etc.. The tissue-specific sections comprise practical instructions on donor screening and tissue

procurement, processing, preservation, storage and transportation related to ocular, amniotic membrane, skin, cardiovascular, and musculoskeletal tissues.

The web-based HOT-SPOT forum is an important supplement to the guidelines. It highlights areas where it is generally acknowledged that greater harmonization is needed, where consensus is lacking on the best practice to be applied, or where it is commonly thought that tools are needed to support improvements in practice. Practical examples and some particular tools for developing areas and where conversations can proceed on specific tissue banking topics are proposed. These HOT-SPOT issues are under regular revision and tissue bankers are urged to participate in the HOT-SPOT discussion on the web page. As consensus is reached and good practice on these topics is more clearly defined, these texts will move into the full guidance document. New hotspot topics will be added as necessary.

The GTPs have drawn upon the work of previously EU-funded projects, particularly the *Sanco-EQSTB* project and the *EUSTITE* project. The *Sanco-EQSTB* project, co-ordinated by Hospital Clinic between 2004 and 2007, published a *Guide of Recommendations for Tissue Banking*¹ defining the fundamental quality and safety key points, a training system for tissue establishment (TE) personnel, a prototype of a tissue registry and a model for auditing TEs (*Guide for Auditing*)². The *EUSTITE* project developed guidance and training for Competent Authority inspectors along with tools and guidance for vigilance and surveillance.

This document has been prepared by drawing upon the European Union Directives on tissue banking and the Good manufacturing practice (GMP) Guidelines, together with text elaborated by the partners of the project from their own experience and knowledge and, in some cases, by building on professional society or nationally agreed standards.

¹ DG Sanco Project. Agreement No 2003209

² DG Sanco Project. Agreement No 2003209

SECTION A: GENERAL REQUIREMENTS

A.1. PERSONNEL

1. *'Every tissue establishment shall designate a responsible person who shall at least fulfil the following conditions and have the following qualifications:*

- a) *possession of a diploma, certificate or other evidence of formal qualifications in the field of medical or biological sciences awarded on completion of a university course of study or a course recognised as equivalent by the Member State concerned;*
- b) *at least two years' practical experience in the relevant fields.*

2. *The person designated in paragraph 1 shall be responsible for:*

- a) *ensuring that human tissues and cells intended for human applications in the establishment for which that person is responsible are procured, tested, processed, stored and distributed in accordance with this Directive and with the laws in force in the Member State;*
- b) *providing information to the competent authority or authorities as required in Article 6;*
- c) *implementing the requirements of Articles 7, 10, 11, 15, 16 and 18 to 24 within the tissue establishment.*

3. *Tissue establishments shall inform the competent authority or authorities of the name of the responsible person referred to in paragraph 1. Where the responsible person is permanently or temporarily replaced, the tissue establishment shall immediately inform the competent authority of the name of the new responsible person and the date on which the duties of that person commence.³*

4. Donor screening responsibilities should include, but not be limited to, the following functions:

- a) To ensure the traceability of the donor during the screening process;
- b) To guarantee that the established periods of time and circumstances have been kept from death to detection, donor refrigeration has been done until recovery and the analytical samples have been taken.
- c) To ensure that the (family / personal/living donor) interview has been performed according to established requirements and to guarantee that there are no discrepancies with other evaluation reports;
- d) To ensure communication with the competent judicial authority in case of unnatural or conspicuous causes of death;

³ Directive 2004/23/EC of the European Parliament and of the Council (Arti 17)

- e) To ensure that medical, social, physical and biological evaluations have been performed according to the established requirements;
- f) To ensure that the absolute rejection criteria are met and the relative exclusion criteria are assessed against safety, quality and availability aspects of the tissue;
- g) To establish the requirements for testing (parameters and methods) and to guarantee that the tests are carried out accordingly (quality agreement, audit visit, etc. when applicable);
- h) To verify the identification, integrity and suitability of the test samples sent to the corresponding laboratory units and that these laboratory are authorised centres by the competent authorities;
- i) To verify that, in case of suspicious and unexpected findings during donor evaluation, an adequate additional investigation is done;
- j) To systematically check the donation dossier review process and adapt the processes when indicated;
- k) To perform a process efficacy review, including an analysis of potential donors, real donors, causes to reject a potential donor and all the statistics considered helpful to improve the detection system and increase the donation efficacy;
- l) To oversee and coordinate feedback with the hospitals or facilities that have reported the donor;
- m) To medically supervise the personnel involved in donor screening;
- n) To guarantee that all legal and ethical aspects have been respected during every donor screening step (informed consent, death diagnosis, etc.).
- o) To control, revise and update all the donor selection criteria documents affecting the donation. These responsibilities may be delegated to another authorized person.

5. Recovery responsibilities should include, but not be limited to, the following functions:

- a) Check donor identification;
- b) Check medical-legal data of the donor documentation;
- c) Donor physical exam (not required for living donors);
- d) Donor preparation (preoperative disinfection and operative field setting) (not required for living-donor tissue-recovery personnel);
- e) Recovery process and inspection of the cavities (thorax, abdomen) during recovery;
- f) Tissue packaging and identification;
- g) Donor reconstruction (not required for living-donor tissue-recovery personnel);
- h) Microbiological sampling;
- i) Transport;

These responsibilities may be performed by a delegated person.

6. Processing responsibilities should include, but not be limited to, the following functions:

- a) Ensure that the tissues / cells for which that person is responsible have been processed, tested, stored and distributed in accordance with the corresponding approved procedures, specifications submitted to the competent authorities, the principles of the ‘European Good Tissue Practices’ and the laws in force in the Member State;
- b) Ensure that the tissues / cells imported from third countries have been processed and checked according to an equivalent quality system and standards respecting the requirements stated in the corresponding European Directives before they are distributed;
- c) Providing information to the competent authority or authorities;
- d) Implementing the requirements of Articles 7, 10, 11, 15, 16 and 18 to 24 (Directive 2004/23/EC) within the TE;
- e) Approval of procedures, their updates and verification of their implementation;
- f) The establishment of a quality assurance programme and verification of the entrusted quality and safety levels;
- g) The release of tissues and cells, the distribution and dispensing of tissues and cells;
- h) Ensure the independency between the quality control results assessment and the processing activities to guarantee the reliability and robustness of the release procedure. The individual(s) in charge of quality control results assessment are strongly recommended not to be involved in the conduct of the process being assured;
- i) Relations with the TE or ORHAs (Organization Responsible for Human Application) and retrieval teams as well as with third subcontracted parties;

These responsibilities may be performed by a delegated person.

7. Biovigilance responsibilities should include, but not be limited to, the following functions:

- a) Report to their own Competent Authority and to any organisation in any country (TE / Recovery Unit) to whom the TE has supplied implicated tissues / cells, if this adverse event or reaction meets the criteria for reporting to a CA (see below);
- b) Where the implicated tissues or cells originated from an organisation (TE or Recovery Unit) in another EU Member State, (and the incident has / may have implications for them), also report to this organisation;

- c) Where the implicated tissues or cells originated from an organisation (TE or Recovery Unit) outside the EU (and the incident has / may have implications for them), also report to this organisation which should take appropriate action in line with their own vigilance system;
- d) Providing detailed information in appropriate language to the Recovery Unit, Transplant Centre, other relevant tissue and/or cells establishment using the tissues or cells, on how to report adverse events or reactions;
- e) Co-ordination of the investigation and evaluation of any reported suspected adverse reaction, involving appropriate stakeholders. This should include allocating grades for Severity, Imputability and Impact Assessment;
- f) Evaluation of any serious adverse event (SAE) in collaboration with appropriate stakeholders, including allocating an Impact score and reporting to the Competent Authority if the criteria are met;
- g) Investigation of the cause and outcome of any serious adverse event or serious adverse reaction (SAE/SAR), collaborating as necessary with other organisations involved, and provision of the investigation report findings back to the Competent Authority;
- h) Proposing a conclusion for each suspected adverse event or reaction and reporting this to the Competent Authority;
- i) Implementation of any corrective or preventive actions arising, including initiation and coordination of recall or quarantine of associated tissues and cells, as appropriate;
- j) Maintenance of records of SAE and SAR reported and investigated;
- k) When tissues or cells are received with a defect in safety or quality from a TE or Recovery Unit, report it as an adverse event to the relevant TE or Recovery Unit;
- l) When a report of an adverse reaction in a recipient is received, report it in accordance with the national requirements for biovigilance. Moreover, if this adverse reaction is suspected to have been caused by a defect of safety or quality in the tissues or cells, report it also to the supplying TE or Recovery Unit;
- m) Initiation and co-ordination of recall or quarantine of associated tissues and cells, as appropriate;

These responsibilities may be performed by a delegated person.

8. *Tissue establishments shall inform the competent authority or authorities of the name of the responsible person referred to in paragraph 1. Where the responsible person is permanently or temporarily replaced, the tissue establishment shall immediately inform the competent authority of the name of the new responsible person and the date on which the duties of that person commence.⁴*

Personnel directly involved in activities relating to the procurement, processing, preservation, storage and distribution of tissues and cells in a tissue establishment shall be qualified to perform such tasks and shall be provided with the training referred to in Article 28(c).⁵

9. *The personnel in tissue establishments must be available in sufficient number and be qualified for the tasks they perform. The competency of the personnel must be evaluated at appropriate intervals specified in the quality system.*

10. *All personnel should have clear, documented and up-to-date job descriptions. Their tasks, responsibilities and accountability must be clearly documented and understood.*

11. *Personnel must be provided with initial/basic training, updated training as required when procedures change or scientific knowledge develops and adequate opportunities for relevant professional development. The training programme must ensure and document that each individual:*

- a) *has demonstrated competence in the performance of their designated tasks;*
- b) *has an adequate knowledge and understanding of the scientific/technical processes and principles relevant to their designated tasks; 25.10.2006 EN Official Journal of the European Union L 294/37;*
- c) *understands the organisational framework, quality system and health and safety rules of the establishment in which they work; and*
- d) *is adequately informed of the broader ethical, legal and regulatory context of their work.⁶*

⁴ Directive 2004/23/EC of the European Parliament and of the Council (Arti 17)

⁵ Directive 2004/23/EC of the European Parliament and of the Council (Arti 18)

⁶ Commission Directive 2006/86/EC (Annex 1)

A.2. FACILITIES AND EQUIPMENT

A.2.1. FACILITIES, EQUIPMENT AND MATERIALS FOR RECOVERY

A.2.1.1. Facilities

A.2.1.1.1. General

1. *'Procurement shall take place in appropriate facilities, following procedures that minimise bacterial or other contamination of procured tissues and cells.'*⁷
2. Procurement should take place in appropriate facilities, following procedures that guarantee the anonymity of the donor.
3. Access to the facilities where the recovery, or any process that could affect the recovery process (e.g. gowning room, materials storage, pre-recovery areas, etc.), is carried out, should be controlled by restricting entrance only to authorized personnel. Access should be strictly controlled once recovery operations have begun.
4. The area where the recovery is performed should have sufficient space and adequate conditions to allow a safe operation and to prevent any contamination of the tissues retrieved and the samples taken.

A.2.1.1.2. Operating room

1. The temperature, humidity and ventilation of the facilities where the donor is manipulated should be adequate so as not to negatively affect the donor.
4. Temperature, humidity and pressure should be controlled. The temperature ranging from $22 \pm 3^\circ\text{C}$ and humidity ranging from $50 \pm 20\%$ are recommended. The pressure should allow the airflow from the cleanest area to the lowest level of cleanliness. A pressure gradient of 15 Pa should be guaranteed with the surrounding areas which should be kept in an adequate level of cleanliness.
2. It is highly recommended that the facilities where the recovery takes place should be provided with an environmental control system to ensure at least a GMP D grade classification in 'at rest' situations. It should guarantee the donor manipulation and examination, manipulation of the material and equipment and a comfortable working conditions during tissue procurement and packaging.

⁷ Commission Directive 2006/17/EC (Art. 2)

3. This classification should be guaranteed by establishing adequate procedures and schedules. The objective of airborne particles monitoring is to ensure that the facilities fulfil the sufficient level of cleanliness just before processing. Therefore these monitoring operations should be scheduled to be performed immediately before the processing activities.
5. The operational parameters of the operating room should be checked at least annually. This qualification should include at least the integrity test of the absolute filters, incoming air flow and air renovation per hour measurement, differential pressures measurement, airborne particles count, temperature and relative humidity measurement and classification recuperation time.
6. The facilities should be properly cleaned, maintained and designed and located getting the maximum protection against contamination and animal pests.
7. The cleaning programme should take into account the initial cleaning just before any recovery process, the cleaning between recovery processes and the cleaning after a recovery process. An adequate alternation of disinfectants should be established and the efficacy of the cleaning procedures should be demonstrated by validation studies.

A.2.1.1.3. Unusual place of recovery

When the recovery takes place in an unusual place (e.g. mortuary, funeral home, donor residence, hospital bed), an enclosed space should be prepared considering the asepsis.

A.2.1.1.4. Ancillary areas

1. The ancillary areas should be fixed to a cleaning programme that minimises the risk of incoming contamination to the operating room.
2. *'Rest and refreshment rooms should be separate from other areas.*
3. *Facilities for changing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not directly communicate with recovery or storage areas⁸.*

A.2.1.2. Equipment

1. *Procurement equipment shall be managed in accordance with the standards and specifications laid down in the directives and with due regard to relevant national and international regulation, standards and guidelines covering the sterilisation of medicines and medical devices. Qualified, sterile instruments and procurement devices shall be used for*

⁸ EU Good Manufacturing Practices Guidelines

tissue and cell procurement. The appropriate equipment and instruments should be used, in order to guarantee the quality of the specific recovered tissue.

2. *Wherever possible, only CE marked medical devices must be used and all concerned staff must have received appropriate training on the use of such devices.*
3. *Sterile instruments and devices must be used for tissue and cell procurement. Instruments or devices must be of good quality, validated or specifically certified and regularly maintained for the procurement of tissues and cells.*
4. *When reusable instruments must be used, a validated cleaning and sterilisation procedure for removal of infectious agents should be in place.⁹*
5. The TE or ORHA must have equipment adapted to the operations for which they are intended, in accordance with the requirements of this general quality standard and in accordance with the standard specific for each tissue type.
6. Measuring, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained. The parameters affecting the quality or safety of tissues and cells (e.g. temperature, pressure, particle count) are defined, monitored and recorded. When appropriate, the equipment will be provided with an alarm system.
7. Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the donors. They should be cleaned and, where applicable, disinfected according to detailed SOPs. They will be inspected regularly and maintenance will be performed according to manufacturer's instructions and / or to the specifications established by the TE or ORHA.
8. After any major repair or modification, the equipment or critical equipment should be re-checked and validated before its release.
9. Calibration and maintenance operations should be carried out according to written procedures and scheduled on an annual basis. Temperature should be monitored with calibrated probes to ensure that during the entire period of time the range has been properly kept.
10. If there is any electronic system in place to manage environmental conditions or any donor data, a validation study of the system should be assessed.

⁹ Directive 2006/17/EC of the European Parliament and of the Council (Annex IV)

A.2.1.3. Materials

1. *Procurement materials and equipment shall be managed in accordance with the standards and specifications laid down in Annex IV, section 1.3 of Commission Directive 2006/17/EC, and with due regard to relevant national and international regulation, standards and guidelines covering the sterilisation of medicines and medical devices. Qualified, sterile instruments and procurement devices shall be used for tissue and cell procurement.*¹⁰
2. The specifications of the materials used to perform any evaluation of the donor should be described and these materials should not have any negative impact on the maintenance of the donors and reliability of the evaluation results.
3. *Specifications for starting and primary or printed packaging materials should include, if applicable:*
 - a) *a description of the materials, including:*
 - i. *the designated name and the internal code reference;*
 - ii. *the reference, if any, to a pharmacopoeia monograph;*
 - iii. *the approved suppliers and, if possible, the original producer of the products;*
 - iv. *a specimen of printed materials.*
 - b) *directions for sampling and testing or reference to procedures;*
 - c) *qualitative and quantitative requirements with acceptance limits;*
 - d) *storage conditions and precautions;*
 - e) *the maximum period of storage before re-examination.*¹¹
4. The TE or ORHA must have the materials adapted for their intended use, in accordance with the requirements of this general standard of quality and, when appropriate, in accordance with the tissues specific standards.
5. When the materials have an influence on the quality or safety of tissues and cells, they should be validated.

A.2.1.4. Safety and Environment

1. The working environment must be safe and conform to labour laws. Data on this subject can be mentioned in the manual.
2. In order to minimize the risk for the staff and/or for the environment, residues of human tissues and cells during their transformation must be destroyed in a specific and traceable way

¹⁰ Commission Directive 2006/17/EC (Art. 2)

¹¹ EU Good Manufacturing Practices Guidelines

in accordance with current legal regulations concerning the disposal of clinical waste. The removal of discarded tissue will follow the same procedure.

A.2.2. FACILITIES, EQUIPMENT AND MATERIALS FOR PROCESSING

A.2.2.1. Facilities

A.2.2.1.1. General

1. The facilities of the tissue bank should be, both in organization and size, in accordance to the activities they are used for. They should be designed in accordance with the general safety requirements of this guide and with the specific requirements for each tissue type.
2. Different areas with specific requirements and maintenance procedures must be defined and, in particular as regards:
 - a) The reception area;
 - b) Processing areas of tissue or cells;
 - c) Packaging and labelling area;
 - d) The conservation area and storage (released, quarantine and rejected);
 - e) Distribution area;
 - f) Laboratory quality control (if applicable);
 - g) Archive;
 - h) Administrative area.
3. Access to various areas of work is strictly limited to authorized persons.
4. *Premises should be situated in an environment which, when considered together with measures to protect the processing, presents minimal risk of causing contamination of materials or tissues/cells.*
5. *Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of tissues/cells. They should be cleaned and, where applicable, disinfected according to detailed written procedures.*
6. *Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the tissues / cells during their processing and storage, or the accurate functioning of equipment.*
7. *Pipework, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses which are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the processing areas.*

8. Drains should be of adequate size, and have trapped gullies. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection.
9. Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.
10. Steps should be taken in order to prevent the entry of unauthorised people.
11. Processing, storage and quality control areas should not be used as a right of way by personnel who do not work in them.
12. Premises should preferably be laid out in such a way as to allow the processing to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels. The flow of personnel, tissues and cells, waste materials and consumables should be described.¹²
13. When biological risk exists (viral inactivation, virus removal, processing with live organisms), cross contamination control may require additional precautions with relation to facilities and equipment, such as the use of dedicated facilities and equipment, processing on a campaign basis and the use of closed systems.

A.2.2.1.2. Processing area

1. 'A tissue establishment must have suitable facilities to carry out the activities for which accreditation / designation / authorisation or licensing is sought.'
2. When these activities include processing of tissues and cells while exposed to the environment, this must take place in an environment with specified air quality and cleanliness in order to minimise the risk of contamination, including cross-contamination between donations. The effectiveness of these measures must be validated and monitored.
3. Unless otherwise specified in following paragraphs, where tissues or cells are exposed to the environment during processing, without a subsequent microbial inactivation process, an air quality with particle counts and microbial colony counts equivalent to those of Grade A as defined in the following paragraphs is required¹³.
4. In case of GMP accreditation, the background environment should be Grade B with a subsequent background of grade D. A risk assessment could be used by the TE to define the

¹² EU Good Manufacturing Practices Guidelines

¹³ Commission Directive 2006/86/EC (Annex I)

background if not working according to GMP (see the provided tool in the hot topics ‘Recovery’).

5. *A less stringent environment than specified previously may be acceptable where:*

- a) *a validated microbial inactivation or validated terminal sterilisation process is applied;*
- b) *or, where it is demonstrated that exposure in a Grade A environment has a detrimental effect on the required properties of the tissue or cell concerned;*
- c) *or, where it is demonstrated that the mode and route of application of the tissue or cell to the recipient implies a significantly lower risk of transmitting bacterial or fungal infection to the recipient than with cell and tissue transplantation;*
- d) *or, where it is not technically possible to carry out the required process in a Grade A environment (for example, due to requirements for specific equipment in the processing area that is not fully compatible with Grade A);¹⁴*
- e) See specific paragraphs on each type of tissue/cells for other requirements

6. *In all cases an environment must be specified. It must be demonstrated and documented that the chosen environment achieves the quality and safety required, at least taking into account the intended purpose, mode of application and immune status of the recipient. Appropriate garments and equipment for personal protection and hygiene must be provided in each relevant department of the tissue establishment along with written hygiene and gowning instructions.*

7. *Processing areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the tissues / cells handled, to the operations undertaken within them and to the external environment.*

8. If there is recirculation of air into the processing areas, appropriate measures should be taken to control risks of contamination.

9. *When the activities for which accreditation / designation / authorisation or licensing is sought involve storage of tissues and cells, the storage conditions necessary to maintain the required tissue and cell properties, including relevant parameters such as temperature, humidity or air quality, must be defined.*

10. *Critical parameters (e.g. temperature, humidity, air quality) must be controlled, monitored, and recorded to demonstrate compliance with the specified storage conditions.*

¹⁴ Commission Directive 2006/86/EC (Annex I)

11. Storage facilities must be provided that clearly separate and distinguish tissues and cells prior to release / in quarantine from those that are released and from those that are rejected, in order to prevent mix-up and cross-contamination between them. Physically separate areas or storage devices or secured segregation within the device must be allocated in both quarantine and released storage locations for holding certain tissue and cells collected in compliance with special criteria.

12. The tissue establishment must have written policies and procedures for controlled access, cleaning and maintenance, waste disposal and for the re-provision of services in an emergency situation.¹⁵

A.2.2.1.3. Environmental airborne control

1. Unless any other requirement is indicated in the specific paragraphs for each type of tissues / cells the following requirements should be satisfied:

2. The processing activities should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency.

3. Clean areas are classified according to the required characteristics of the environment. Each processing operation requires an appropriate environmental cleanliness level in the operational state in order to minimise the risks of particulate or microbial contamination of the tissue/cells or materials being handled.

4. Four grades can be distinguished:

a) Grade A: Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position in open clean room applications. The maintenance of laminarity should be demonstrated and validated. A uni-directional air flow and lower velocities may be used in closed isolators and glove boxes;

b) Grade B: This is the background environment for the grade A zone if tissues or cells are processed according to GMP rules. The risk assessment tool for defining the air quality can be used to select the background;

c) Grade C and D: Clean areas for carrying out less critical stages according to documented risk assessment in the processing activities.

5. The maximum permitted airborne particle concentration for each grade is given in the following table.

¹⁵ Commission Directive 2006/86/EC (Annex I)

	<i>Maximum permitted number of particles per m³ equal to or greater than the tabulated size</i>			
	<i>At rest</i>		<i>In operation</i>	
<i>Grade</i>	<i>0.5 µm</i>	<i>5 µm</i>	<i>0.5 µm</i>	<i>5 µm</i>
<i>A</i>	3520	20	3520	20
<i>B</i>	3520	29	352000	2900
<i>C</i>	352000	2900	3520000	29000
<i>D</i>	3520000	29000	<i>Not defined*</i>	<i>Not defined*</i>

*When the limit of number of particles is not defined, each tissue establishment should do it according to a risk assessment study.

6. The ‘at-rest’ state is the condition where the installation is installed and operating, complete with processing equipment but with no operating personnel present. The ‘in operation’ state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.¹⁶
7. The ‘at rest’ requirements should be respected in all cases. The ‘in operation’ requirements are only applicable to sterile operations.
8. For classification purposes in Grade A zones, a minimum sample volume of 1m³ should be taken per sample location. For classification purposes EN/ISO 14644-1¹⁷ methodology defines both the minimum number of sample locations and the sample size based on the class limit of the largest considered particle size and the method of evaluation of the data collected.
9. Portable particle counters with a short length of sample tubing should be used for classification purposes because of the relatively higher rate of precipitation of particles $\geq 5.0 \mu\text{m}$ in remote sampling systems with long lengths of tubing. Isokinetic sample heads should be used in unidirectional airflow systems.
10. ‘In operation’ classification may be demonstrated during normal operations, simulated operations or during media fills as worst-case simulation is required for this. EN ISO 14644-2 provides information on testing to demonstrate continued compliance with the assigned cleanliness classifications.

¹⁶ EU Good Manufacturing Practices Guidelines

¹⁷ Cleanrooms and associated controlled environments -- Part 1: Classification of air cleanliness

11. The rules of particle count cannot be achieved when for example bone is aseptically processed. Less stringent conditions may then be applied when it is not technically possible to carry out the required process in a Grade A environment with risk assessment or to include in the processing sterilisation or inactivation process.

11. Clean rooms and clean air devices should be routinely monitored in operation, if applicable, and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean air devices.

12. For Grade A zones, when 'in operation' requirements are applicable, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, e.g. live organisms and radiological hazards. In such cases, monitoring during routine equipment set-up operations should be undertaken prior to exposure to the risk. Monitoring during simulated operations should also be performed. The Grade A zone should be monitored at such a frequency and with suitable sample size so that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded. It is accepted that it may not always be possible to demonstrate low levels of $\geq 5.0 \mu\text{m}$ particles at the point of fill when filling is in progress, due to the generation of particles or droplets from the tissue/cells itself.

13. It is recommended that a similar system be used for Grade B zones although the sample frequency may be decreased. The importance of the particle monitoring system should be determined by the effectiveness of the segregation between the adjacent Grade A and B zones.

14. The Grade B zone should be monitored at such a frequency and with suitable sample size that changes in levels of contamination and any system deterioration would be captured and alarms triggered if alert limits are exceeded.

15. Airborne particle monitoring systems may consist of independent particle counters; a network of sequentially accessed sampling points connected by manifold to a single particle counter; or a combination of the two. The system selected must be appropriate for the particle size considered. Where remote sampling systems are used, the length of tubing and the ratio of any bends in the tubing must be considered in the context of particle losses in the tubing.

16. The sample sizes taken for monitoring purposes using automated systems will usually be a function of the sampling rate of the system used. It is not necessary for the sample volume to be the same as that used for formal classification of clean rooms and clean air devices.

17. In Grade A and B zones, the monitoring of the $\geq 5.0 \mu\text{m}$ particle concentration count takes on a particular significance as it is an important diagnostic tool for early detection of failure. The occasional indication of $\geq 5.0 \mu\text{m}$ particle counts may be false counts due to electronic noise, stray light, coincidence, etc. However, consecutive or regular counting of low levels is an indicator of a possible contamination event and should be investigated. Such events may indicate early failure of the HVAC system, equipment failures or may also be diagnostic of poor practices.

18. The particle limits given in the table for the ‘at rest’ state should be achieved after a short ‘clean up’ period of 15-20 minutes (guidance value) in an unmanned state after completion of operations.

19. The monitoring of Grade C and D areas in operation should be performed in accordance with the principles of quality risk management. The requirements and alert/action limits will depend on the nature of the operations carried out, but the recommended ‘clean up period’ should be attained.

20. Other characteristics such as temperature and relative humidity depend on the product and nature of the operations carried out. These parameters should not interfere with the defined cleanliness standard.¹⁸

A.2.2.1.4. Environmental microbiological control

1. When ‘in operation’ requirements are applicable, microbiological monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations. Additional microbiological monitoring is also required outside processing operations, e.g. after validation of systems, cleaning and sanitisation.

¹⁸ EU Good Manufacturing Practices Guidelines

2. When ‘in operation’ requirements are not applicable, microbiological monitoring should be performed with the aim of ensuring an adequate aseptic grade to initiate any processing activities. A monitoring program should be established accordingly.

3. *The maximum permitted limits for each grade is given in the following table.*

Recommended limits for microbial contamination (a)				
Grade	air sample cfu/m³	settle plates (diameter 90 mm) cfu/4hours (b)	contact plates (diameter 55 mm) cfu/plate	glove print 5 fingers cfu/glove
<i>A</i>	1	1	1	1
<i>B</i>	10	5	5	5
<i>C</i>	100	50	25	-
<i>D</i>	200	100	50	-

Notes

(a) These are average values.

(b) Individual settle plates may be exposed for less than 4 hours.

4. Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded operating procedures should prescribe corrective action.¹⁹

A.2.2.1.5. Sanitation

1. The sanitation of clean areas is particularly important. They should be cleaned thoroughly in accordance with a written programme. Where disinfectants are used, more than one type should be employed and rotation-use of disinfectants is recommended. Monitoring should be undertaken regularly in order to detect the development of resistant strains.

2. Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilised. Disinfectants and detergents used in Grades A and B areas should be sterile prior to use.

3. Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.²⁰

4. Maximum permitted microbiological limits for each cleanliness grade after cleaning and sanitation should be specified.

A.2.2.1.6. Isolator technology

¹⁹ EU Good Manufacturing Practices Guidelines

²⁰ EU Good Manufacturing Practices Guidelines

1. *The utilisation of isolator technology to minimize human interventions in processing areas may result in a significant decrease in the risk of microbiological contamination of aseptically processed tissues/cells from the environment. There are many possible designs of isolators and transfer devices. The isolator and the background environment should be designed so that the required air quality for the respective zones can be realised. Isolators are constructed of various materials more or less prone to puncture and leakage. Transfer devices may vary from a single door to double door designs to fully sealed systems incorporating sterilisation mechanisms.*
2. *The transfer of materials into and out of the unit is one of the greatest potential sources of contamination. In general, the area inside the isolator is the local zone for high risk manipulations, although it is recognised that laminar air flow may not exist in the working zone of all such devices.*
3. *The air classification required for the background environment depends on the design of the isolator and its application. It should be controlled and for aseptic processing it should be at least grade D.*
4. *Isolators should be introduced only after appropriate validation. Validation should take into account all critical factors of isolator technology, for example the quality of the air inside and outside (background) the isolator, sanitisation of the isolator, the transfer process and isolator integrity.*
5. *Monitoring should be carried out routinely and should include frequent leak testing of the isolator and glove/sleeve system.²¹*

A.2.2.1.7. Ancillary areas

1. *The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimise the risk of confusion between different tissues/cells, to avoid cross-contamination and to minimise the risk of omission or wrong application of any of the processing or control steps.*
2. *Restrooms, control rooms and refreshment rooms should be separate from other areas.*
3. *Facilities for changing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not directly communicate with processing or storage areas.*

²¹ EU Good Manufacturing Practices Guidelines

4. Maintenance workshops should as far as possible be separated from processing areas.
5. Whenever parts and tools are stored in the processing area, they should be kept in rooms or lockers reserved for that use.²²

A.2.2.2. Equipment

1. Processing equipment should be designed, located and maintained to suit its intended purpose.
2. Repair and maintenance operations should not present any hazard to the quality of the tissues and cells.
3. Processing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition.
4. Washing and cleaning equipment should be chosen and used in order not to be a source of contamination.
5. Equipment should be installed in such a way as to prevent any risk of error or of contamination.
6. Processing equipment should not present any hazard to the tissues and cells. The parts of the processing equipment that come into contact with the tissues/cells must not be reactive, additive or absorptive to such an extent that it will affect the quality of the tissues/cells and thus present any hazard.
7. Balances and measuring equipment of an appropriate range and precision should be available for processing and control operations.
8. Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.
9. Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.
10. Distilled, deionized and, where appropriate, other water pipes should be sanitised according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

²² EU Good Manufacturing Practices Guidelines

- 11. Defective equipment should, if possible, be removed from processing and quality control areas, or at least be clearly labelled as defective.*
- 12. The services that could impact on the tissues/cells quality (i.e. compressed air, heating, ventilating and air conditioning) should be qualified and scheduled in a maintenance programme.*
- 13. Calibration and maintenance operations should be carried out according to written procedures and scheduled on an annual basis.*
- 14. Should there be any electronic system in place to manage environmental conditions or any processing quality data, a validation study should be assessed.²³*

A.2.2.3. Materials

A.2.2.3.1. General

1. The TE must have the equipment and materials according to the activities to which they are designed and in accordance with the general safety requirements of this Guide and the specific requirement of each tissue type.
2. All equipment and materials affecting the quality and safety of the tissues and cells must be defined and validated.
3. All incoming materials should be checked to ensure that the consignment corresponds to the order.
- 4. Specifications for starting and primary or printed packaging materials should include, if applicable:*
 - a) a description of the materials, including:*
 - i. the designated name and the internal code reference;*
 - ii. the reference, if any, to a pharmacopoeia monograph;*
 - iii. the approved suppliers and, if possible, the original producer of the products;*
 - iv. a specimen of printed materials.*
 - b) directions for sampling and testing or reference to procedures;*
 - c) qualitative and quantitative requirements with acceptance limits;*
 - d) storage conditions and precautions;*
 - e) the maximum period of storage before re-examination.²⁴*

²³ EU Good Manufacturing Practices Guidelines

5. A standardized written procedure (SOP) will regulate the specific media that come into contact with tissues and cells during processing, the addition of therapeutic products to tissues and cells, the choice of those media and products, their characteristics, their source and control and the rules for asepsis and labelling. A procedure to select the materials must be in place. Defined specifications and functions of the media; validate the effect of media or other materials on the functional characteristics of the tissues. New batches must be tested.

6. When using processing media and / or added therapeutic products, their source, lot number and expiration date must be listed in the documentation of the different stages of processing.

A.2.2.3.2. Material requirements

1. The following aspects should be attended to regarding reagents used during the processing of tissues and cells:

- a) Free of viral contamination (certificate should be available);
- b) Free of TSE contamination (certificate should be available);
- c) Produced under GMP conditions when possible;
- d) For human use when possible;
- e) Identity, purity, sterility and quantification of endotoxins should be defined;
- f) Human and animal origin reagents should be substituted when possible;
- g) Antibiotics should be avoided when possible;
- h) Final residues of reagents should be quantified when possible;
- i) Risk assessment of reagent residues should be done.

A.2.2.4. Safety and Environment

1. It should be ensured that the safety of the working environment is according to other safety regulations.

2. Residues of human tissues and cells during their transformation must be destroyed in a specific and traceable way to minimize the risk to the staff involved in transformation and to the environment in accordance with local laws and national regulations in force concerning the disposal of clinical waste.

3. Waste materials and liquids used during processing should be utilised in accordance with local laws and national regulations in force concerning the disposal of medical material waste.

²⁴ EU Good Manufacturing Practices Guidelines

A.2.3. FACILITIES, EQUIPMENT AND MATERIALS FOR STORING

1. The devices intended for storage should be located preferably in a separate area to which access is controlled and restricted to authorized persons.
2. A temperature monitoring system should be utilized to document temperatures and to alert staff when temperatures have strayed outside acceptable limits. Procedures should be in place for reviewing temperatures. If storage utilizes liquid nitrogen, either liquid nitrogen levels or temperature should be monitored and documented at an interval specified in the SOP.

A.3. DONOR SCREENING

1. Both generic and specific GTPs should include requirements related to donor selection and evaluation, risk assessment, validation methodologies, documentation, premises, personnel and quality management.
2. The major objective of the chapter on the donor screening process is to protect the final tissue recipient. Safety and quality of the human tissue depends, to a large extent, on the ability to identify true positive risks and avoid false positive risks.
3. According to EU Directive 2006/17/EC, Articles 3 and 4 '*Selection criteria for donors are based on an analysis of the risks related to the application of the specific cells/tissues. Indicators of these risks should be identified by physical examination, review of the medical and behavioural history, biological testing, post-mortem examination (for deceased donors) and any other appropriate investigation.*' Outlines for physical examination are described elsewhere in this Guide, whereas the other criteria could be defined as the process of donor screening. The purpose of screening a donor is to collect information, to assess the data on critical points of safety, quality and unique identification, and to evaluate this information in relation to relevant aspects of the tissue, in order to determine whether or not to release tissues for transplantation purposes
4. This chapter aims to provide tools to carry out the screening test in the best way so as to ensure the quality of the tissue and the safety of transplant recipients. The scope of this chapter covers the steps between donor detection and donor release for further processing.

A.3.1. ACTIVITIES

A.3.1.1. Donor detection

1. A system to ensure that any deceased individual can be detected in an adequate period of time to perform an effective donation should be established between the TEs and the corresponding TE or ORHAs.
2. The TEs and the TE or ORHAs should establish a written agreement where the responsibilities of each party are defined.
3. The TE or ORHAs should perform an analysis of the potential donors, real donors, causes to reject a potential donor and all the statistics considered helpful to improve the detection system and increase donation efficacy.
4. The process efficacy review should be performed at least annually.
5. It is advisable to create a database shared by TE or ORHAs, TEs and blood establishments. A list of donors rejected by a blood establishment due to blood analysis results may be helpful for tissue and organs centres.

A.3.1.1.1. *Determination of death*

1. The determination of death and the death certificate of a donor have to be based on the irreversible cessation of the cardio-respiratory functions (heart death) and encephalic functions (brain death).
2. The certification of death criteria will conform to the Member State's regulation.
3. The death of the non-heart beating donor (NHBD) must be certified by a doctor independent of the retrieval team. In case of deceased heart beating donors (HBD), it is necessary to take into account the relevant legislation related to determination of brain death.

A.3.1.1.2. *Donor identification*

1. *Member States shall establish a system for the identification of human tissues and cells, in order to ensure the traceability of all human tissues and cells²⁵.*
2. A codification system, physical and documental and / or electronic, should be in place to guarantee traceability and biovigilance from donor screening until tissue transplantation (e.g. the donor is identified with a wrist band and/or different labels attached to the body). Both identification methods include the donor number. The donor code is applied to all tissues obtained after recovery.

²⁵ Directive 2004/23/EC of the European Parliament and of the Council (Art 25)

3. The coding system should be designed so as to relate all transplants of a certain donor to a unique donor number in order to guarantee traceability and biovigilance from donor screening until tissue transplantation.
4. A (potential) donor should receive a donor identification number before any further procedures are started. All documental and/or electronic data that are collected from this donor, should state this number. All body materials (e.g. blood, tissue, fluid) that are collected from this donor, have to refer to the donor number.
5. The method of verifying the donor's identity should be described in an identification procedure. This procedure should be followed before starting the recovery and should enable the identity of the donor to be established beyond any doubt. The verification should be performed based on at least two independent factors like date of birth and name, or name and hospital patient number.
6. The source of the donor's identity has to be documented. For living donors this could mean taking the number of the identity card. For deceased donors, the presence of toe tags, wrist bands or other confirmation of the deceased's identity should be noted.
7. A reliable identification of the deceased donor must always take place before starting the recovery.

A.3.1.1.3. Post Morten donor maintenance

1. To avoid deterioration of the corpse of a deceased donor, the body has to be brought into a cooled environment as soon as possible. The eyes should be closed in case of cornea donation.
2. If the donor has not been cooled within six hours after death, the recovery should have commenced within 12 hours after heart death, unless a later time can be determined based on the tissue specific quality aspects.
3. If the refrigeration (1-10°C) takes place during the first six hours, the recovery may start as late as 12 hours after death. The maximum recovery delay has to be established per tissue type, based on the quality and contamination aspects of the specific tissue and the way it will be processed.
4. When the tissues derives from an organ donor, the corpse is maintained at a temperature >35°C until the recovery of organs. When the tissue recovery is performed immediately after

organ donation, the corpse does not have to be refrigerated. If not, the corpse is kept at 1-10°C until the recovery.

5. Specific maximum time limits for recovery of different types of tissues and cells are incorporated into specific sections of quality.

6. The sampling of blood for testing must always be as short as possible. The analytical samples should be taken within 24 hours after death to avoid the damage by cytological processes, unless validation of the post mortem testing allows otherwise.

	Sampling	Refrigeration (around 4°C) after death	Recovery after death
NHBD	≤ 24 hours	≤ 6 hours	≤ 24 hours
		>6 hours or not refrigerated	≤ 12 hours
HBD	At the moment of the death diagnosis At the beginning of the organs recovery	Not necessary if recovery is performed immediately after organs retrieval	After organ recovery, (≤ 12 hours after aortic cross clamp)
		If refrigerated after organ retrieval	
		≤ 6 hours from aortic cross clamp	≤ 24 hours from aortic cross clamp
		>6 hours from aortic cross clamp	≤ 12 hours from aortic cross clamp
LIVING DONOR	At the time of donation -7 days after donation	N/A	N/A

A.3.1.2. Donor consent; judicial and familiar

1. Member States shall, in keeping with their national legislation, take all necessary measures to ensure that donors, their relatives or any persons granting authorisation on behalf of the donors are provided with all appropriate information as referred to in the Annex.²⁶

²⁶ Directive 2004/23/EC of the European Parliament and of the Council (Art 13)

2. Before the procurement of tissues and cells proceeds, an authorised person must confirm and record: (a) that consent for the procurement has been obtained in accordance with Article 13 of Directive 2004/23/EC; and (b) how and by whom the donor has been reliably identified.²⁷

3. Evidence of consent or lack of opposition should be documented in the donor file.
4. The consent for all type of donors should be based on understandable information which at least contains items according to the table below

Explanation of the purposes of donation	Types of tissue that can be donated and general descriptions of the use of tissue transplants Possible use for research or educational purposes Possible involvement of for-profit organisations Possible use for patients in other parts of Europe Alternatives for treatment when no donation takes place.
Explanation of the risks or consequences of tissue donation	Physical consequences and risk of bodily harm Relation with burial arrangements Relation with autopsy and autopsy results Relations with investigation of Medical examiner/Coroner
Explanation of the process of donation	Time frame of the donation decision process Time frame of the procurement and processing of tissue Need for information of the patient's medical and social history Need for testing of blood samples for tissue transmissible diseases (Presumed) authorisation for the requirement of these data/testing Description of the recovery and the possible reconstruction of the body including physical appearance Information of possible movement of the donor General information about processing/storage and distribution including risk of rejection of tissue.
Information, confidentiality and record keeping	Confidentiality of the medical / social information Option for communication of the results of testing, donor screening and transplantation with the donor /next of kin/GP or treating physician including the protection of the privacy of patients Record keeping for 30 years after transplantation Contact data of the tissue bank/ tissue bank representatives

²⁷ Commission Directive 2006/17/EC (Annex IV)

	Explanation of costs involved and the fact that no charge will be made for the process.
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A.3.1.2.1. *Deceased donor*

1. There should be an authorized person who confirms and records that consent has been obtained specifying organs or tissue donation, and for transplant or research purposes. A clear differentiation should be done if consent is obtained from a living donor or a deceased donor.
2. Each country should take into account that different systems apply for obtaining consent for transplantation: an opting out system or opting in systems. For both systems, a registry should be created in order to check if the person was opposed to donation when alive (opting-out) or showed the wishes to donate (opting-in).
3. The contents of the familiar interview should include, but not be limited to:
 - a) The medical personnel, in collaboration with the responsible physician, will inform the family of the circumstances that have caused the death of the patient, ensuring the understanding of the explained facts. Then, the transplant coordinator conducts the interview to obtain family consent, and guide the family in their questions or problems relating to the donation.
 - b) The interview will be held respecting the privacy and intimacy of the family or the living donor.
 - c) The scope and the purposes of the donation should be explained in detail and agreed with the family or the living donor. Regarding deceased consent, different types should be differentiated:
 - i. Donation of organs, tissues or both;
 - ii. Donation for transplantation;
 - iii. Donation of tissues for research with clinical application;
 - iv. Donation of tissues for research with no clinical application;
 - v. Donation of tissues for research and pharmaceutical manipulation and posterior marketing.
4. The medical / social evaluation should be performed during the interview if necessary, in the terms described in the paragraph 1.26. The general (and tissue specific) exclusion criteria are used to determine whether tissues are suitable for donation or not. In order to avoid any

risk factors from transmissible diseases or behaviour, there should be a questionnaire addressed to the donor family.

- a) Medical records should show that all exclusion criteria have been appropriately investigated and applied.
 - b) According to the EU Directive 2006/17 Annex IV the social history has to be sought from an individual that has known the donor well. Mostly this is the reporting physician. If this is not the case, this could be:
 - i. General practitioner
 - ii. Other treating physician
 - iii. Family
 - iv. Friends
 - c) In case the social history cannot be traced with some certainty, the donor has to be rejected. The social history contains information on the potential donor's lifestyle, (e.g. alcohol abuse, use of drugs and other intoxications); if there is reason to suspect that the patient was at risk of a sexually transmitted disease, such as HIV, Hepatitis, etc., this forms a general contra-indication. Information on travel history is also sought.
5. In case a legal process applies; judicial consent will be obtained according to local regulations before starting any recovery activities. When judicial authorization is needed due to an unknown cause of death, the transplant coordinator will be the person responsible to ask consent from the judge on call and in charge of the investigation. Recovery will only carried out if it does not affect the judicial autopsy.
6. *'All information must be given and all necessary consents and authorisations must be obtained in accordance with the legislation in force in Member States.'*
7. *'The confirmed results of the donor's evaluation must be communicated and clearly explained to the relevant persons in accordance with the legislation in Member States.'*²⁸

A.3.1.2.2. Living donor

- 1. Informed consent shoukd be obtained for living donors. The informed consent should include an explanation, in understandable terms, of all the reasonable risk and potential harm, both for the donor and recipient, as well as all the tests to be performed. '*The health professional responsible for obtaining the health history must ensure that the donor has:*

- a) *understood the information provided;*
 - b) *had an opportunity to ask questions and been provided with satisfactory responses;*

²⁸ Directive 2004/23/EC of the European Parliament and of the Council (Annex)

c) confirmed that all the information provided is true to the best of his/her knowledge.

2. Information must be given prior to the procurement.

3. The information must be given by a trained person able to transmit it in an appropriate and clear manner, using terms that are easily understood by the donor.

4. The information must cover: the purpose and nature of the procurement, its consequences and risks; analytical tests, if they are performed; recording and protection of donor data, medical confidentiality; therapeutic purpose and potential benefits and information on the applicable safeguards intended to protect the donor.

5. The donor must be informed that he/she has the right to receive the confirmed results of the analytical tests, clearly explained.

6. Information must be given on the necessity for requiring the applicable mandatory consent, certification and authorisation in order that the tissue and/or cell procurement can be carried out.²⁹

7. In case of minors donors or donor with no legal capacity the permission should be obtained from parents or legal representative.

A.3.1.3. Data protection and confidentiality

1. Member States shall take all necessary measures to ensure that all data, including genetic information, collated within the scope of this Directive and to which third parties have access, have been rendered anonymous so that neither donors nor recipients remain identifiable.

2. For that purpose, they shall ensure that:

a) data security measures are in place, as well as safeguards against any unauthorised data additions, deletions or modifications to donor files or deferral records, and transfer of information;

b) procedures are in place to resolve data discrepancies;

c) no unauthorised disclosure of information occurs, whilst guaranteeing the traceability of donations.

²⁹ Commission Directive 2004/33/EC (Annex II)

3. Member States shall take all necessary measures to ensure that the identity of the recipient(s) is not disclosed to the donor or his family and vice versa, without prejudice to legislation in force in Member States on the conditions for disclosure, notably in the case of gametes donation³⁰.

4. Besides autologous donation, anonymity between donor and recipient and vice versa must be strictly maintained. An exception may exist for a living related donation. An anonymous identification coding system of donation of tissues and cells must guarantee anonymity and traceability in the case of allogeneic donations.

A.3.1.4. Advertising

1. Member States shall take all necessary measures to ensure that any promotion and publicity activities in support of the donation of human tissues and cells comply with guidelines or legislative provisions laid down by the Member States. Such guidelines or legislative provisions shall include appropriate restrictions or prohibitions on advertising the need for, or availability of, human tissues and cells with a view to offering or seeking financial gain or comparable advantage.

2. Member States shall endeavour to ensure that the procurement of tissues and cells as such is carried out on a non-profit basis.³¹

A.3.1.5. Prohibition of financial compensation for donors

1. Member States shall endeavour to ensure voluntary and unpaid donations of tissues and cells. Donors may receive compensation, which is strictly limited to making good the expenses and inconveniences related to the donation. In that case, Member States define the conditions under which compensation may be granted.

2. Member States shall endeavour to ensure that the procurement of tissues and cells as such is carried out on a non-profit basis.

3. The donation of tissues and cells must be voluntary and unpaid. No financial gain or any other compensation can be done to the living donor or the deceased donor's family. In case of unrelated living donors, an allowance to cover any costs incurred can be accepted.³²

³⁰ Directive 2004/23/EC of the European Parliament and of the Council (Art.13)

³¹ Directive 2004/23/EC of the European Parliament and of the Council (Art.12)

³² Directive 2004/23/EC of the European Parliament and of the Council (Art.12)

4. The extra medical costs incurred by the consideration of a deceased as a tissue donor (e.g. serological / bacteriological) cannot be charged to the donor. These charges should be assumed by the tissue bank and never charged to the donor.

A.3.1.6. Donor evaluation; medical, social and physical

A.3.1.6.1. General

1. *The activities related to tissue procurement shall be carried out in such a way as to ensure that donor evaluation and selection is carried out in accordance with the requirements referred to in Article 28(d) and (e) and that the tissues and cells are procured, packaged and transported in accordance with the requirements referred to in Article 28(f).*

2. *In the case of an autologous donation, the suitability criteria shall be established in accordance with the requirements referred to in Article 28(d).*

3. *The results of the donor evaluation and testing procedures shall be documented and any major anomalies shall be reported in accordance with the requirements referred to in the Annex.*

4. *The competent authority or authorities shall ensure that all activities related to tissue procurement are carried out in accordance with the requirements referred to in Article 28(f).*

5. *The competent authority or authorities shall take all necessary measures to ensure that tissue and cell procurement complies with the requirements referred to in Article 28(b), (e) and (f). The tests required for donors shall be carried out by a qualified laboratory accredited, designated, authorised or licensed by the competent authority or authorities.*

6. *An authorised person must collect and record the donor's relevant medical and behavioural information according to the requirements described in section 1.4.*

7. *In order to acquire the appropriate information, different relevant sources must be used, including at least an interview with the donor, for living donors, and the following when appropriate:*

- a) *the medical records of the donor;*
- b) *an interview with a person who knew the donor well, for deceased donors;*
- c) *an interview with the treating physician;*
- d) *an interview with the general practitioner;*
- e) *the autopsy report.*

8. In addition, in the case of a deceased donor, and in the case of a living donor when justified, a physical examination of the body must be performed to detect any signs that may be sufficient in themselves to exclude the donor or which must be assessed in the light of the donor's medical and personal history.

9. The complete donor records must be reviewed and assessed for suitability and signed by a qualified health professional.³³

10. The donor selection criteria should be based on the risk analysis associated with the properties and use of tissues and cells. Physical examination, medical history and social behaviour, biological testing, post-mortem examination (for deceased donors) and other appropriate investigations provide the information to assess the presence of such risks.

11. The donor selection criteria should take into account those donor aspects that influence the safety of the donor and the safety and quality of a specific tissue.

12. Tissue specific contra-indications for donation have to be determined by the responsible person of the TE, based on the risk assessment linked to the given disorder.

13. The TE should have a procedure in place to evaluate the consequence for donor selection of emerging (infectious) diseases or advancing medical insights. Evaluations have to be documented.

14. An authorised person must collect and record the donor's relevant medical and behavioural information according to the requirements.

15. In order to acquire the appropriate information, different relevant sources must be used, including at least an interview with the donor for living donors, and for deceased donors an interview with a person who knew the donor well. Furthermore, the following sources when appropriate:

- a) Medical records of the donor;
- b) Interview with the treating physician;
- c) Interview with the general practitioner;
- d) Autopsy report when applicable;
- e) Results of laboratory or imaging investigations;
- f) Medical information of the mother in case of a newborn donor.

16. 'The health professional responsible for obtaining the health history must ensure that the donor or other relevant party has:

- a. understood the information provided;
- b. had an opportunity to ask questions and been provided with satisfactory responses

³³ Commission Directive 2006/17/EC (Annex IV)

c. confirmed that all the information provided is true to the best of his/her knowledge.³⁴ (Commission Directive 2006/17/EC, Annex IV Art 1.1.2)

17. In addition, in the case of a deceased donor, and in that of a living donor when justified, a physical examination of the body must be performed to detect any signs that may be sufficient in themselves to exclude the donor or which must be assessed in the light of the donor's medical and personal history.
18. A qualified health professional assesses the available donor information for the presence of contraindications, before starting the recovery procedure.
19. The complete donor records must be reviewed and assessed for the absence of donor rejection criteria before release of the tissue for transplantation and signed by an authorized physician.
20. All donor data should be recorded and kept for 30 years after the use of the donated tissue. Data should be protected from unauthorized viewing

A.3.1.6.2. Medical and social evaluation

1. The evaluation of the donor should contain all the necessary medical and social information to assess the presences of the following aspects:
 - a) General contraindications concerning the safety of all donated tissue as stated in Directive 2004/23/EC Annex I.
 - b) Additional safety related contraindications that are the result of risk assessments arising from health risks related to processing, donor population characteristics, emerging infectious diseases, or other relevant factors.
 - c) Tissue specific contraindications that involve the quality of the donated tissue.
2. The final determination of the criteria for exclusion for tissue donation is the responsibility of the responsible person, in consultation with a medical advisor or medical advisory committee, if needed. A list of mandatory and optional contraindications could be;

Medical evaluation	
Weight and height NTS (pre-screening)	If no exact weight and height are known, an estimate will suffice.
Active systemic infections and vaccinations NTS (pre-screening)	This includes all systemic infections (bacterial, viral, parasitical, prions). Various circumstances are possible including: <ol style="list-style-type: none">1. An infection at the time of death. Please report:

³⁴ Commission Directive 2006/17/EC (Anex IV)

	<ul style="list-style-type: none"> ▪ the type of infection ▪ lab results ▪ whether cultures have been taken, including (provisional) results ▪ antibiotic treatment, including duration and effectiveness of the treatment and if any, the results of the treatment (e.g. fever-free period). <ol style="list-style-type: none"> 2. Suspicion of a systemic infection without supportive diagnostics. Please report the symptoms on which the suspicions are based. 3. In case clinical signs are not highly suspect for an infection but infection cannot be ruled out, please report as such. 4. Systemic infections of which the patient has been cured, but the cause is still (possibly latent) present (e.g. polio, hepatitis B-C, syphilis) 5. Report vaccinations given with live attenuated virus, such as polio, mumps, measles, rubella and post exposure rabies vaccinations. <p>The criteria used to assess whether sepsis is present are in accordance with the internationally guidelines.</p>
Clinical evidence or suspicion of neurodegenerative diseases with unknown aetiology, or other disorders possibly caused by prions NTS (pre-screening)	The following apply: <ul style="list-style-type: none"> ▪ All non-vascular or unexplained forms of dementia, such as Alzheimer's disease; ▪ ALS, multiple sclerosis, Parkinson ▪ variant CJD or risk factors for prion disease such as familial CJD, the use of growth hormone and stay in the UK during 1980-1996.
Haematological malignancies or other haematological disorders NTS (pre-screening)	All lymphoproliferative, myeloproliferative and other haemopoietic disorders, such as leukaemia, Morbus Kahler, non-Hodgkin disease, polycythaemia vera and aplastic anaemia.
Other malignancies. NTS (pre-screening)	Present at time of death or in the medical history.
Infection or signs of infection	All, also local, infections or signs of infection such as lab results, positive cultures, infiltration on X-thorax. Treatment with antibiotics? <i>Infections can be a tissue specific contraindication.</i>
Bone marrow suppression due to medication in the last three months	Medication administered within three months before death with a proven bone marrow depression. Mention which medication, indication, dose and last lab. results (Hb, leucocytes and platelets)
Chronic use of	Relevant in case of chronic use for more than six weeks.

corticosteroids	Provide details on indication, dosage and duration of use. <i>Use of corticosteroids can be a <u>tissue specific contraindication</u>.</i>
Other medication	Please report all other medications that have been used.
Infusions and transfusions within the previous 48 hours	Only relevant if given for blood loss. Please report type and quantity of all infused fluids (blood products, colloids, crystalloids, plasma replacement, plasma expanders etc.), as well how much and time of the infusions/transfusions
Social evaluation	
Presence of risk factors for HIV, HTLV, Hepatitis B or C	<p>This group includes donors belonging to known risk groups (either directly or through their sexual partners):</p> <ul style="list-style-type: none"> - Persons who have used non-medical drugs intranasally in the last five years. - Persons who have <u>ever</u> injected non-medical drugs (intravenous, intramuscular or subcutaneous). - Persons with haemophilia or related clotting disorders who have received human-derived clotting factor concentrates before 1987. - Men who have had sex with another man in the preceding five years. - Men and women who have engaged in sex in exchange for money or drugs in the preceding five years. - Persons emigrated from countries where transfer of HIV infection through heterosexual contacts plays an important role in the spreading of the HIV virus, like countries in South East Asia, Caribbean and in countries in Africa below the Sahara. Unless person has been in the Netherlands longer than one year and in that time has not been back to an endemic region. - Persons that, in the past six months, had sexual contact with persons of one of the above mentioned groups or were sexual partners of persons who are infected with HIV, HTLV or hepatitis C or B or who are suspected thereof. - Persons that, in the preceding six months, were exposed to (possibly) infected blood via accidental percutaneous puncture or through contact with an open wound and non-intact skin or mucous membrane. - Persons who are diagnosed or treated for SOA in past six months. - Children of 18 months or younger born to mothers with risk of HIV, or children from these mothers who were breastfed. - Tattoo: if the donor has had a tattoo, piercing or needle accident in the previous 6 months, there may be a reason for not accepting. Please contact the BIS doctor on duty for evaluation. Piercings made with the use of shared needles or genital piercings shall not be

	<p>accepted.</p> <ul style="list-style-type: none"> - Persons who have jaundice of unknown but possibly infectious origin. - Persons who are in 'Close contact' with another individual with infectious hepatitis, such as shared household (kitchen and toilet) or sexual partner during the last six months. <p>Intermittent haemodialysis</p>
Intoxications	<p>Includes alcohol abuse, drug abuse and long term exposure to heavy metals such as lead, mercury, chromium, arsenic, pesticides. Nicotine abuse is not relevant.</p>
Risk of tropical diseases, for example as a result of travel.	<p>Report risk for emerging diseases contracted during travel to foreign countries, such as SARS, Avian Flu, Malaria, Yellow fever etc.</p> <p>Mention: which country, duration and date period of stay, vaccinations.</p> <p>If unknown report as such.</p>
Travel/Visit to the United Kingdom	<p>Report if known whether duration of stay was longer than six months and between January 1980 and December 1996.</p> <p>If unknown report as such.</p>

3. For every potential donor, anamnestic data must be obtained from the available relevant sources, such as the living donor's treating physician, general practitioner, next of kin or in the case of a deceased, other people who knew the donor well, and / or the donor's medical record included in the donor file.
4. When questioning donors or their relatives, it must be established that the phrasing of the questions is understood by the respondent.

A.3.1.6.3. Physical evaluation of cadaveric donors

1. The evaluation of the cadaveric donor should include a physical examination to detect signs:
 - a) that are in themselves sufficient to exclude the donor; or
 - b) that may be an indication for further investigations; or
 - c) are a contraindication for donation, when assessed in the light of the donor's medical and social history.
2. The physical examination has to be performed by trained personnel, in a working area with sufficient light, and under the condition that the entire body surface is easily accessible for examination by the retrieval staff.

3. A written report on the findings during the physical examination should consist minimally of a check list of specific signs that have to be looked for. Findings should also be drawn on a diagram of the body.

4. An example is given of a list of signs and their associated contraindications that indicate a (potential) cause for rejection of the donor for donation.

General impression

Describe the degree of care of the donor _____

Inspection of the skin	Description (including localisation, dimensions, type/aspect, signs of infection)		
Jaundice	<input type="checkbox"/> No	<input type="checkbox"/> Yes	_____
Tattoos / piercings	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<u>Old / new</u> _____
Non-therapeutic needle wounds	<input type="checkbox"/> No	<input type="checkbox"/> Yes	_____
Skin abnormalities / petechiae	<input type="checkbox"/> No	<input type="checkbox"/> Yes	_____
Traumas / wounds / scars	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<u>Old / new</u> _____
Lines (arterial / venous)	<input type="checkbox"/> No	<input type="checkbox"/> Yes	_____

Specific inspection of

Head / neck

Head / neck Abnormalities of eyes/sclera No Yes Already enucleated

Abnormalities of oral cavity

Other facial abn. (e.g. infectious) No Yes

Pathological lymph nodes No Yes _____
(> 1 cm or abnormal consistency)

Abn. of the ears (e.g. CSF, blood) No Yes

Torso & extremities

Enlarged liver / spider naevi No Yes

Pathological lymph nodes No Yes _____
(> 1 cm or abnormal consistency)

Indications for auto-immune/
connective tissue conditions No Yes _____

Fractures No Yes

GenitaliaAbnormalities of the genitalia No Yes _____**Inspection of the rear side of the body**Skin abnormalities No Yes _____Peri-anal abnormalities No Yes _____**A.3.1.6.4. Exclusion criteria****A.3.1.6.5.1. Deceased donor**

1. Cause of death unknown, unless autopsy provides information on the cause of death after procurement and none of the general criteria for exclusion set out in the present section applies.

2. History of a CNS disease of unknown aetiology.

3. Presence, or previous history, of malignant disease, except for primary basal cell carcinoma, carcinoma *in situ* of the uterine cervix, and some primary tumours of the central nervous system that have to be evaluated according to scientific evidence. Donors with malignant diseases can be evaluated and considered for cornea donation, except for those with retinoblastoma, haematological neoplasm, and malignant tumours of the anterior segment of the eye.

4. Risk of transmission of diseases caused by prions. This risk applies, for example, to:

- a) people diagnosed with Creutzfeldt-Jakob disease, or variant Creutzfeldt-Jacob disease, or having a family history of non-iatrogenic Creutzfeldt-Jakob disease;
- b) people with a history of rapid progressive dementia or degenerative neurological disease, including those of unknown origin;
- c) recipients of hormones derived from the human pituitary gland (such as growth hormones) and recipients of grafts of cornea, sclera, limbal cells / ossicular tympanomeatal allograft and dura mater, and persons that have undergone undocumented neurosurgery (where dura mater may have been used).³⁵

For variant Creutzfeldt-Jakob disease, further precautionary measures may be recommended.

5. Specific precautionary measures regarding VCJD:

³⁵ Commission Directive 2006/17/EC (Annex I)

- a) Any person who stayed in Britain for six months or more between 1980 and 1996 (cumulatively) will be excluded as a donor.

6. Specific precautionary measures regarding prions diseases:

- a) The removal of tissue is excluded from:
- i. potential donors with a transmissible spongiform encephalopathy confirmed or detected as probable;
 - ii. potential donors with the presence or suspicion of a degenerative central nervous system including those of unknown origin;
 - iii. potential donors with a family history of CJD, Gerstmann-Scheinker disease or fatal familial insomnia;
 - iv. potential donors with a history of intracranial surgery (craniotomy syn.);
 - v. potential donors who have received treatment based on growth hormones extracted from human hypophyses;
 - vi. potential donors who underwent implantation of ocular tissue;
 - vii. potential donors who underwent implantation of dura mater allograft;
 - viii. potential donors who underwent implantation of an ossicular tympanomeatal allograft.

7. *Systemic infection which is not controlled at the time of donation, including bacterial diseases, systemic viral, fungal or parasitic infections, or significant local infection in the tissues and cells to be donated. Donors with bacterial septicaemia may be evaluated and considered for eye donation but only where the corneas are to be stored by organ culture to allow detection of any bacterial contamination of the tissue.*

8. *History, clinical evidence, or laboratory evidence of HIV, acute or chronic hepatitis B (except in the case of persons with a proven immune status), hepatitis C and HTLV I/II, transmission risk or evidence of risk factors for these infections.*

9. *History of chronic, systemic autoimmune disease that could have a detrimental effect on the quality of the tissue to be retrieved.*

10. *Indications that test results of donor blood samples will be invalid due to:*

- a) *the occurrence of haemodilution, according to the specifications in Annex II, section 2, where a pre-transfusion sample is not available;*
- b) *treatment with immunosuppressive agents.*

11. *Evidence of any other risk factors for transmissible diseases on the basis of a risk assessment, taking into consideration donor travel and exposure history and local infectious disease prevalence.*

12. *Presence on the donor's body of physical signs implying a risk of transmissible disease(s) as described in Annex IV, point 1.2.3.*

13. *Ingestion of, or exposure to, a substance (such as cyanide, lead, mercury, gold) that may be transmitted to recipients in a dose that could endanger their health.³⁶*

14. Recent vaccination with living attenuated viruses whereby a risk for transmission can be suspected

15. *Transplantation with xenografts.*

A.3.1.6.5.2. Additional exclusion criteria for dead children donors

1. *Any children born from mothers with HIV infection or that meet any of the exclusion criteria described in the previous section must be excluded as donors until the risk of transmission of infection can be definitely ruled out.*

2. *Children aged less than 18 months born from mothers with HIV, hepatitis B, hepatitis C or HTLV infection, or at risk of such infection, and who have been breastfed by their mothers during the previous 12 months, cannot be considered as donors regardless of the results of the analytical tests.*

3. *Children of mothers with HIV, hepatitis B, hepatitis C or HTLV infection, or at risk of such infection, and who have not been breastfed by their mothers during the previous 12 months and for whom analytical tests, physical examinations, and reviews of medical records do not provide evidence of HIV, hepatitis B, hepatitis C or HTLV infection, can be accepted as donors.³⁷*

A.3.1.6.5.3. Living donors

A.3.1.6.5.3.1. Allogeneic use donation

1. *Allogeneic living donors must be selected on the basis of their health and medical history, provided on a questionnaire and through an interview performed by a qualified and trained healthcare professional with the donor, in compliance with point 4.*

2. *This assessment must include relevant factors that may assist in identifying and screening out persons whose donation could present a health risk to others, such as the possibility of transmitting diseases or health risks to themselves.*

³⁶ Commission Directive 2006/17/EC (Annex I)

³⁷ Commission Directive 2006/17/EC (Annex I)

3. For any donation, the collection process must not interfere with or compromise the health or care of the donor. In the case of cord blood or amniotic membrane donation, this applies to both mother and baby.
4. Selection criteria for allogeneic living donors must be established and documented by the tissue establishment (and the transplanting clinician in the case of direct distribution to the recipient), based on the specific tissue or cells to be donated, together with the donor's physical status and medical and behavioural history and the results of clinical investigations and laboratory tests establishing the donor's state of health.
5. The same exclusion criteria must be applied as for deceased donors with the exception of those concerning to the unknown cause of death. Depending on the tissue or cell to be donated, other specific exclusion criteria may need to be added, such as:

- a) pregnancy (except for donors of umbilical cord blood cells and amniotic membrane and sibling donors of haematopoietic progenitors)
- b) breastfeeding
- c) in the case of haematopoietic progenitor cells, the potential for transmission of inherited conditions³⁸

A.3.1.6.5.3.2. Autologous use donation

1. If the removed tissues and cells are to be stored or cultured, the same minimum set of biological testing requirements must apply as for an allogeneic living donor. Positive test results will not necessarily prevent the tissues or cells or any product derived from them being stored, processed and reimplanted, if appropriate isolated storage facilities are available to ensure no risk of cross contamination with other grafts and/or no risk of contamination with adventitious agents and/or mix ups.³⁹

A.3.1.6.6. Autopsy

1. If an autopsy of the donor has been required, the responsible doctor will examine the results before tissue release.

A.3.1.7. Donor evaluation; biological

A.3.1.7.1. General

1. The tests must be carried out by a qualified laboratory, authorised as a testing centre by the competent authority in the Member State, using CE-marked testing kits where

³⁸ Commission Directive 2006/17/EC (Annex II)

³⁹ Commission Directive 2006/17/EC (Annex I)

appropriate. The type of test used must be validated for the purpose in accordance with current scientific knowledge.

2. The biological tests will be carried out on the donor's serum or plasma; they must not be performed on other fluids or secretions such as the aqueous or vitreous humour unless specifically justified clinically using a validated test for such a fluid.

3. When potential donors have lost blood and have recently received donated blood, blood components, colloids or crystalloids, blood testing may not be valid due to haemodilution of the sample. An algorithm must be applied to assess the degree of haemodilution in the following circumstances:

- a) **ante-mortem** blood sampling: if blood, blood components and/or colloids were infused in the 48 hours preceding blood sampling or if crystalloids were infused in the hour preceding blood sampling;*
- b) **post-mortem** blood sampling: if blood, blood components and/or colloids were infused in the 48 hours preceding death or if crystalloids were infused in the hour preceding death.*

4. TEs may accept tissues and cells from donors with plasma dilution of more than 50 % only if the testing procedures used are validated for such plasma or if a pre-transfusion sample is available.

5. In the case of a deceased donor, blood samples must have been obtained just prior to death or, if not possible, the time of sampling must be as soon as possible after death and in any case within 24 hours after death. The testing method for cadaveric blood samples must be validated for cadaveric blood.

6. In the case of living donors (except allogeneic bone marrow stem-cell and peripheral blood stem-cell donors, for practical reasons), blood samples must be obtained at the time of donation or, if not possible, within seven days post donation (this is the 'donation sample').

7. Where tissues and cells of allogeneic living donors can be stored for long periods, repeat sampling and testing is required after an interval of 180 days. In these circumstances of repeat testing, the donation sample can be taken up to 30 days prior to and 7 days post donation.

8. Where tissues and cells of allogeneic living donors cannot be stored for long periods and repeat sampling is therefore not possible, point 6 above applies.

9. If in a living donor (except bone marrow stem-cell and peripheral blood stem-cell donors) the 'donation sample', as defined in point 6 above, is additionally tested by the nucleic acid amplification technique (NAT) for HIV, HBV and HCV, testing of a repeat blood sample is

not required. Retesting is also not required if the processing includes an inactivation step that has been validated for the viruses concerned.

10. In the case of bone marrow and peripheral blood stem-cell collection, blood samples must be taken for testing within 30 days prior to donation.

11. In the case of neonatal donors, the biological tests may be carried out on the donor's mother to avoid medically unnecessary procedures upon the infant.

12. In the case of living donors, see tissue specific paragraphs.⁴⁰

A.3.1.7.2. Allogeneic Donation

A.3.1.7.2.1. Heart beating donors

1. The following biological tests must be performed for all heart beating donors as a minimum requirement:

- a) Anti-HIV 1 and 2 has to be negative (a positive test is a reason for exclusion);
- b) HBs Ag has to be negative (positive test is a reason for exclusion);
- c) Anti-HBc: if HBsAg test is negative and anti-HBc is positive, an anti-HBs test will be made. If the test is also positive, it can be considered that the donor has recovered from a past infection, and the tissue can therefore be used. If, by contrary, anti-HBs are negative or doubtful, then it should be rejected as a donor;
- d) Anti-HCV has to be negative (a positive test is a reason for exclusion);
- e) Testing for syphilis: a validated test result has to be negative (positive serological test is a reason for exclusion).

Table 1.

Serology test	Grounds for testing	Accepted result
S-TrpaAb	Exclusion of syphilis	Negative
S-HIV 1/2Ab	Exclusion of HIV	Negative
S-HIV Ag	Exclusion of HIV	Negative
S-HbsAg	Exclusion of acute HBV	Negative
S-HbcAb	Exclusion of past HBV	Negative
		Positive → HBsAb → Positive
S-HCVAb	Exclusion of acute or past HCV	Negative
HIV1 NAT	Exclusion of acute HIV infection	Negative (not detectable)
HBV NAT	Exclusion of acute HBV infection	Negative (not detectable)
HCV NAT	Exclusion of acute HCV infection	Negative (not detectable)

⁴⁰ Commission Directive 2006/17/EC (Annex II)

2. Additional tests:

- a) *HTLV-I antibody testing must be performed for donors living in, or originating from, high-incidence areas or with sexual partners originating from those areas or where the donor's parents originate from those areas.*
- b) *A validated testing algorithm must be applied to exclude the presence of active infection with *Treponema pallidum*. A non-reactive test, specific or non-specific, can allow tissues and cells to be released. When a non-specific test is performed, a reactive result will not prevent procurement or release if a specific *Treponema* confirmatory test is non-reactive. A donor whose specimen tests reactive on a *Treponema*-specific test will require a thorough risk assessment to determine eligibility for clinical use.⁴¹*
- c) Anti-CMV: a positive test does not constitute a reason to reject the tissue. However, it is desirable not to use tissue from CMV positive donors in immunosuppressed recipients.
- d) Rh Factor: Some tissue donor Rh (D) positive antigen can sensitize a recipient Rh (D) negative. It is therefore advisable to avoid it in recipients belonging to the age where a pregnancy can still occur. The decision on this issue, however, is the responsibility of the physician in charge of implantation.
- e) In certain circumstances, additional testing may be required depending on the donor's history and the characteristics of the tissue or cells donated (e.g. RhD, HLA, malaria, CMV, toxoplasma, EBV, Trypanosoma cruzi)
- f) Anti-HTLV1 / 2 is recommended in donors who assume the risk.
- g) A second serology (anti-HIV1 and anti-HIV2 and anti-HCV)) is advisable for recipients three months after transplantation (back-screening).

A.3.1.7.2.2. Non-heart beating donors (Post-mortem removal)

1. In case of non-heart-beating donors, serological tests are performed on a blood sample taken within seven days before death (after identification) or by default on a blood sample taken immediately after death and never beyond 24 hours.
2. The minimum serological requirements for HBD are the same as for NHBD. Additional tests, such as HIV1, HCV NAT, Anti-CMV, are recommended for non-heart beating donors in order to have an additional guarantee

A.3.1.7.2.3. Living donors

1. In case of living donors, the first serological tests are performed at the time of donation or seven days after donation when the first option is not possible.

⁴¹ Commission Directive 2006/17/EC (Annex II)

2. Where tissues and cells of allogeneic living donors can be stored for long periods, repeat sampling and testing is required after an interval of 180 days. In these circumstances of repeat testing, the donation sample can be taken up to 30 days prior to and 7 days post donation.⁴²
3. The serological minimum requirements are the same as for deceased donors.
4. In the case of living donors, a guarantee of tissue and cells must be obtained from:
 - a) A test anti-HIV1 / 2 and anti-HCV, retested at least 180 days (six months) after sampling. Only when the results of that test are known and proven to be negative, may the tissue be distributed for implantation: or
 - b) NAT test HIV1, HBV and HCV performed on the sample taken at the time of donation. In this case, it is not necessary to retesting after six months: or
 - c) A validated period of viral inactivation. In this case, it is not necessary to retest after six months.
5. If at least one of three above mentioned conditions is completed, the tissues are kept in quarantine.
6. However, under exceptional circumstances, the doctor responsible for a tissue bank may repeal the quarantine (e.g. medical emergency) after reviewing the case and risk assessment. The decision must be explained decision and the transplant doctor, who can accept or reject the risk, informed.

A.3.1.7.3. Autologous Donations

1. In the case of autologous living donors, it is necessary to perform the same tests (serology) as for an allogeneic donor.
2. A positive result does not automatically exclude these tissues and cells. However, a separate storage system must be provided.

A.3.1.7.4. Serum Bank

1. It is desirable to store the serum in a serum bank in order to complete serological tests that could be needed depending on the evolution of science. The absence of a serum bank for a donation of tissues and cells does not constitute in itself a reason for rejection of these tissues or cells.

A.3.1.8. Documentation and release for recovery

A.3.1.8.1. General

1. The TE or ORHA must develop a system to maintain a record of each donation step; donor selection, collection, control, preparation, storage and distribution of tissues and cells. The

⁴² Commission Directive 2006/17/EC Annex II

decision to release (i.e validation for human use) is taken on the basis of data contained in this dossier.

2. The records and documents must be completed in a legibly and indelibly manner.
3. The dossier and any other documentation can also be saved on a reliable system such as a digital or microfilm system. When data is managed by the TE or ORHA personnel, a declaration must be made to the European Commission responsible for personal data protection according to current regulations.
4. The recording of relevant data in the dossier must allow identification of the author and the date of their entry.
5. Data security and confidentiality must be guaranteed.

A.3.1.8.2. Release

1. The items indicated in the Donor Screening File Contents should be required for the release or rejection of a donor for tissues/cells and thus should be documented. The donor dossier should include the contents showed in Donor Screening File Contents section.

A.3.1.8.3. Donor Screening File Contents

1. The donor record will, at least, contain:
 - a) *The donor identification (first name, family name and date of birth — if a mother and child are involved in the donation, both the name and date of birth of the mother and the name, if known, and date of birth of the child);*
 - b) A unique identification code of the donation given by the TE or ORHA;
 - c) *Age, sex, medical and behavioural history (the information collected must be sufficient to allow application of the exclusion criteria, where required);*
 - d) Cause and certificate of death;
 - e) Type of donor: living donor, NHBD or HBD;
 - f) Type of donation: allogeneic, autologous;
 - g) Evidence of informed consent (living donor): a copy of the original consent signed by the surgeon or the no opposition (deceased donor), as the result of consulting the National Register;
 - h) *Outcome of body examination, where applicable;*
 - i) Identification of the recovery centre and the person responsible for donation and recovery;
 - j) *Haemodilution formula, where applicable;*
 - k) *The consent/authorisation form (familiar and judicial), where applicable;*

- l) Proof of consent for donation of the retrieved tissues/cells and its purpose;
- m) *Clinical data, laboratory test results, and the results of other tests carried out;*
- n) *If an autopsy was performed, the results must be included in the record (for tissues and cells that cannot be stored for extended periods, a preliminary verbal report of the autopsy must be recorded);*
- o) *For haematopoietic progenitor cell donors, the donor's suitability for the chosen recipient must be documented. For unrelated donations, when the organisation responsible for procurement has limited access to recipient data, the transplanting organisation must be provided with donor data relevant for confirming suitability;⁴³*
- p) Date and time of cardiac arrest (for deceased donor);
- q) Cooling time (for non-heart beating donors);
- r) Hospital discharge report, if applicable;
- s) Report of Biovigilance alerts, if applicable;
- t) Identification of the recovery centre and the person responsible for donation and recovery.

2. Other relevant information:

- a) ABO, Rh factor (if applicable);
- b) Serological results (HIV 1 & 2, HBV, HCV) and syphilis;
- c) Additional serological results, if any;
- d) Serum sample in the serum bank (desirable);
- e) Bacteriological results (aerobic and anaerobic) and mycological.

Access to registers and data must be restricted to persons authorised. This File must be kept for a minimum of 30 years after clinical use.

A.3.1.9. Availability for inspection

1. The records must be accessible at any time for inspections conducted by the competent authority. Donor identity and data related to it will be restricted to the sanitary establishment but must, if necessary, be available for inspectors.

A.3.1.10. Traceability

1. The TE or ORHA should be able to assure the traceability of the donor.
2. The traceability requirement applies to all relevant data related to the donor, critical products and materials coming into contact with the donor.

⁴³ Commission Directive 2006/17/EC (Annex IV)

3. Corrections, changes or amendments made to a file should be carried out according to a written change control management procedure.

4. When electronic data is affected any critical change should be recorded and available through an audit trail.

A.4. RECOVERY

A.4.1. ACTIVITIES

1. *The activities related to tissue procurement shall be carried out in such a way as to ensure that donor evaluation and selection is carried out in accordance with the requirements referred to in this text and that the tissues and cells are procured, packaged and transported in accordance with the requirements referred to in the regarding sections.*

2. *In the case of an autologous donation, the suitability criteria shall be established in accordance with the requirements referred to in the regarding sections.*

3. *The competent authority or authorities shall ensure that all activities related to tissue procurement are carried out in accordance with the requirements referred to in the regarding sections.⁴⁴*

4. In order to prevent any infectious disease contamination or cross contamination, the recovery process should not be performed with more than one donor simultaneously unless it is possible to ensure that there is no risk of such contamination.

A.4.1.1. Access to the operating room

1. *For deceased donation, the area of access must be restricted. A local sterile field using sterile drapes must be used. Staff conducting procurement must be clothed appropriately for the type of procurement. Usually, this will extend to being scrubbed, gowned in sterile clothing and wearing sterile gloves, face shields and protective mask.⁴⁵*

2. The personnel should enter the operating room following written gowning procedures. It is advisable to use an airlock as a protection barrier.

3. The materials should enter the operating room with an adequate grade of cleanliness according to D grade classification. It is advisable to use an airlock as a protection barrier or a segregated storage room inside the classified operating room.

⁴⁴ Directive 2004/23/EC of the European Parliament and of the Council (Art.15)

⁴⁵ Commission Directive 2006/17/EC (Annex IV)

4. It is recommended that the donor is moved into the operating room using a specific transport element. The transport element used to move the donor into the operating room should only be used in this area. It is advisable to use an airlock as a protection barrier.

A.4.1.2. Access to an unusual place of recovery

1. For the cadaveric donation, the area of access must be restricted. A local sterile field using sterile drapes must be used. The persons conducting the procurement must be clothed appropriately. Usually, this will extend to being scrubbed, gowned in sterile clothing and wearing sterile gloves, face shields and a protective mask.
2. The personnel should enter the procurement area following written gowning procedures for the respective recovery area.
3. The materials should enter the procurement area after an appropriate description of conditions for tissue recovery in an unusual place of recovery.
4. The donor should be moved into the procurement area using a specific transport element. The transport element used to move the donor into the unusual recovery area should be appropriate to the needs and specification for the respective tissue recovery.

A.4.1.3. Recovery

A.4.1.3.1. General

- 1. The procurement of human tissues or cells shall be authorised only after all mandatory consent or authorisation requirements in force in the Member State concerned have been met.*
- 2. There shall also be SOPs describing the procedures for procurement, packaging, labelling and transportation of the tissues and cells to the point of arrival at the tissue establishment or, in the case of direct distribution of tissues and cells, to the clinical team responsible for their application or, in the case of tissue/cell samples, to the laboratory for testing.⁴⁶*
3. The TE or ORHA must have a written protocol on the practical organization of the donor screening and tissue/cells recovery.
4. When the organization of donor screening and the recovery of tissues and cells are done by a third party, there is a need for a written agreement between that party and the TE or ORHA.

⁴⁶ Commission Directive 2006/17/EC (Art.2)

The contract will determine the type of tissues and cells that must be recovered as well as the protocols that need to be followed. This party must be qualified for this purpose and must have the competent clinical equipment to carry out the recovery of tissues and cells.

5. The recommended general recovery flow is: skin, corneas, cardiovascular and musculoskeletal. Some cardiovascular tissues (femoral arteries) may be recovered at the same time with the musculoskeletal tissues.
6. The tissues/cells retrieval should be performed so as to prevent any contamination during recovery or to increase the risk of disease transmission from donor to recipient. Measures to prevent infectious disease contamination or cross contamination should be established taking into account the possible sources: air contamination, contamination coming from the recovery personnel, contamination coming from the donor (e.g. skin, intestinal bacteria), or contamination of the tissues/cells already recovered.
7. The quality control tests should be described defining the test, the analytical method, the sample size and the acceptance criteria.
8. See specific paragraphs for the minimum evaluation requirements for each kind of tissue.

A.4.1.3.2. Deceased donors

A.4.1.3.2.1. Recovery procedure of tissues

1. The personnel in charge of tissue recovery must have the experience and knowledge specifically needed for each tissue type. Standard operating procedures (SOP's) must be in place to ensure the preservation of the characteristics of the tissues and cells for their final use, and to minimize the risk of microbiological contamination or spreading of transmissible diseases.
2. For this purpose:
 - a) Recovery must be done in conditions equivalent to those in force for surgery;
 - b) The materials and equipment must be disposable or properly sterilised;
 - c) When the recovery of NHBD is carried out in the mortuary, it cannot be done simultaneously with the autopsy and must be done within controlled environmental conditions. It is advisable to recover the tissue before the autopsy takes place.
3. Any special circumstances (such as recovery after autopsy) or any other incident during recovery that can affect the quality of the tissues and cells recovered, must be reported and analysed by the physician in charge of the TE or ORHA.

A.4.1.2.3.2. Reconstruction of the donor's body

1. *Where appropriate, the staff and equipment necessary for body reconstruction of deceased donors shall be provided. Such reconstruction shall be completed effectively.*
2. *Once the tissues and cells have been retrieved from a deceased donor body, it must be reconstructed so that it is as similar as possible to its original anatomical appearance.⁴⁷*
3. The reconstruction of the body must be made respecting the corpse, whatever its final destination.

A.4.1.3.3. Living donors

1. Procurement of tissues and cells from living donors shall take place in an environment that ensures their health, safety and privacy.
2. For recovery of living donors, procedures should be in place for each tissue type and comply with the specific standards of quality. The procedure should ensure the safety of the living donor and minimize the risk of contamination and infection by diseases.
3. The tissues should be retrieved in a way as to fulfil the criteria of the final destination (e.g. quality, length, size etc.), depending on the specific criteria for the type of tissue.

A.4.1.4. Processing during recovery

1. The competent authority or authorities may authorise the direct distribution of specific tissues and cells from where the procurement is carried out to a health care establishment for immediate transplantation. Even in this case, all the tissues should be evaluated according to the specific requirements for each kind of tissue (see specific paragraphs).
2. As long as any tissue/cells processing is performed in the operating room, the grade A surrounded by at least grade D should be respected attending the air quality conditions.. These processing activities should be considered as exceptional situations that should be sufficiently justified in writing, and authorised if required by local regulation.

A.4.1.5. Packaging and labelling

1. The procured tissue must be appropriately inspected and rinsed before the processing in the TE is initiated, so as to avoid the presence of blood that might be a source of bacterial contamination.

⁴⁷ Commission Directive 2006/17/EC (Art.2)

2. Packaging of the procured human body material must be appropriate and conform to the standards for the respective tissue. Double or triple wrapping is necessary, depending on the tissue-specific requirements.

3. A unique identifying code shall be allocated to the donor and the donated tissues and cells, during procurement or at the end of the recovery process, to ensure proper identification of the donor and the traceability of all donated material. The coded data shall be entered in a register maintained for the purpose.

4. *Following procurement, all recovered tissues and cells must be packaged in a manner which minimises the risk of contamination and must be stored at temperatures that preserve the required characteristics and biological function of the cells/tissues. The packaging must also prevent contamination of those responsible for packaging and transportation of the tissues and cells.*

5. *The packaged cells/tissues must be shipped in a container which is suitable for the transport of biological materials and which maintains the safety and quality of the contained tissue or cells.*⁴⁸

The temperature conditions between the recovery and processing must be appropriate to the type of tissue so as to preserve its required characteristics and biological function.

6. *Any accompanying tissue or blood samples for testing must be accurately labelled to ensure identification with the donor, and must include a record of the time and place the specimen was taken.*⁴⁹

7. The type of packaging and labelling for each tissue/cells will be established in the specific tissue type section.

8. All packaging and labelling materials should be stored and managed in a safe manner in order to avoid any cross contamination or mix-up, which could result in incorrectly identified / packaged tissues / cells.

9. Critical printed materials (i.e. primary and secondary packaging and leaflets) should be stored in segregated and access-controlled areas.

10. The respective donor information file should be placed in an envelope, sealed, marked ‘Medical Secret’ and addressed to the TE to which the tissue is destined for processing.

⁴⁸ Commission Directive 2006/17/EC (Annex IV)

⁴⁹ Commission Directive 2006/17/EC (Annex IV)

A.4.1.5.1. Primary packaging and labelling operation

1. The packaging of tissues and cells after recovery must (i) minimize the risk of contamination of tissues and cells (ii) minimize risk of contamination of the persons in charge of transportation and (iii) ensure the necessary conditions (i.e. temperature) for the preservation of the tissues and cells.

Each tissue is packed separately in a sterile packaging as soon as possible after recovery. Double (triple)-packaging should be used when possible.

3. The package is then placed in a suitable container to ensure the preservation of the tissues and cells, and the physical protection of the recovered human material during transportation. It is essential that the container is properly closed and not opened until the graft is received by the TE. The conditions in the container must be appropriate to the standards and conditions for the respective tissue (i.e. temperature and duration of transport to the tissue establishment where the tissue processing will take place).

4. At the time of procurement, every package containing tissues and cells must be labelled. The primary tissue/cell container must indicate the donation identification or code and the type of tissues and cells. Where the size of the package permits, the following information must also be provided:

- a) date (and time where possible) of donation;
- b) Name of the persons involved in the tissue recovery and their coordinates (phone, fax, mail);
- c) Type of the tissues recovered;
- d) Other tissues/cells/organs recovered and eventually their destination;
- e) Blood transfusion before the recovery and hemodilution risk;
- f) hazard warnings;
- g) nature of any additives/transport medium (if used);
- h) in the case of autologous donations, the label must state 'for autologous use only';
- i) in the case of directed donations, the label must identify the intended recipient;

5. If any of the information under points (a) to (e) above cannot be included on the primary package label, it must be provided on a separate sheet accompanying the primary package.⁵⁰

A.4.1.5.2. Secondary packaging and labelling operation

1. When tissues/cells are shipped by an intermediary, every shipping container must be labelled at least with:

- a) TISSUES AND CELLS and HANDLE WITH CARE;

⁵⁰ Commission Directive 2006/17/EC (Annex IV)

- b) the identification of the establishment from which the package is being transported (address and phone number) and a contact person in the event of problems;
- c) the identification of the tissue establishment of destination (address and phone number) and the person to be contacted to take delivery of the container;
- d) the date and time of the start of transportation;
- e) specifications concerning conditions of transport relevant to the quality and safety of the tissues and cells;
- f) in the case of all cellular products, the following indication: DO NOT IRRADIATE;
- g) when a product is known to be positive for a relevant infectious disease marker, the following indication: BIOLOGICAL HAZARD;
- h) in the case of autologous donors, the following indication: 'FOR AUTOLOGOUS USE ONLY';
- i) specifications concerning storage conditions (such as DO NOT FREEZE).⁵¹

A.4.1.6. Storage and transport

A.4.1.6.1. Storage

1. The recovered tissues/cells should be stored in a segregated and designated area following the specific storage conditions for each tissue/cells. (See tissue specific sections)
2. Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials as well as tissues/cells in quarantine, released for processing, rejected, returned, recalled or for investigative use.
3. *Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.*
4. *Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.*⁵²
5. Printed packaging and labelling materials may be considered critical and special attention should be paid to their safe and secure storage.

A.4.1.6.2. Transport

1. The choice of transport mode is made according to general regulations governing transportation. The transportation of tissues is done following a validated procedure

⁵¹ Commission Directive 2006/17/EC (Annex IV)

⁵² EU Good Manufacturing Practices Guidelines

according to the safety and preservation criteria for each tissue type. These conditions are reflected in the tissue specific GTPs.

2. When the temperature must be maintained at a certain level during transportation, maintenance control must be validated first.
3. The maximum transportation time will be determined considering each tissue and cells type. The place, date and time of departure and arrival, packaging integrity at departure and arrival, identity of the person receiving the tissues should be recorded and kept in the TE or ORHA.
4. If the transport is sub-contracted, a written agreement must be signed by the transporter and TE or ORHA.
5. Any transportation must be accompanied by a transport document that will be attached to the file.
6. The date and time of pick up and the date and time of arrival at the destination (TE) must be indicated by the person who carries out the tissue transport.
7. Samples of tissue and blood sampling included in the transport must be carefully identified.

A.4.1.7. Documentation and release for processing

A.4.1.7.1. General

1. The TE or ORHA must develop a system to maintain a record of each step of donation, donor selection, collection, control, preparation, storage and distribution of tissues and cells. The decision to release (validation for human use) is taken on the basis of data contained in this dossier.
2. The records and documents must be completed in a legibly and indelibly manner.
3. The records and any other documentation can also be saved on a reliable system such as a digital or microfilm system. When data are managed by the TE personnel, a declaration must be made to the European Commission responsible for personal data protection according to current regulations.
4. The recording of relevant data in the record must allow the identification of the author and the date of these entries.
5. Data security and confidentiality must be guaranteed.

A.4.1.7.2. Release

1. The items indicated in the Recovery File Contents should be required for the release or rejection of the tissues/cells and thus should be documented. The tissue/cells recovered dossier should include the contents presented in the Recovery File Contents paragraph.
2. The responsible TE should make the final decision on the tissue release or rejection on the basis of the following criteria:
 - a) donor information concerning his behaviour conditions;
 - b) donor acceptance/rejection criteria (age, post mortem delay, exclusion clinical criteria);
 - c) donor informed consent;
 - d) the tissue related criteria (morphology, processing conditions, storage conditions);
 - e) the quality control of the donor blood (bacteriological and virology analyses) and tissue (bacteriology, histology).

A.4.1.7.3. Recovery File Contents

1. *The organisation performing the procurement must produce a procurement report, which is passed on to the tissue establishment. This report must contain at least:*
 - a) The Donor Screening File and/or release statement of Donor Screening Responsible Person with an analysis of all exclusion criteria for the respective tissue donation;
 - b) The transfusion of blood products or other solutions during last 24 to 48 hours and estimation of the risk for hemodilution;
 - c) *The identification, name and address of the tissue establishment to receive the cells/tissues;*
 - d) *Donor identification data (including how and by whom the donor was identified);*
 - e) *Description and identification of procured tissues and cells (including samples for testing) and the institution to which the other tissues, organs or cells are dedicated;*
 - f) *Identification of the person who is responsible for the procurement session, including signing;*
 - g) *Date, time (where relevant, start and end) and location of procurement and procedure (SOP) used, including any incidents that occurred; where relevant, environmental conditions at the procurement facility (description of the physical area where procurement took place);*
 - h) *For deceased donors, conditions under which the cadaver is kept: refrigerated (or not), time of start and end of refrigeration;*
 - i) *ID/batch numbers of reagents and transport solutions used;*⁵³

⁵³ Commission Directive 2006/17/EC (Annex IV)

2. *The report must also contain the date and time of death where possible.*

3. *The date and time of procurement may be included, where possible.⁵⁴*

Access to registers and data must be restricted to authorised persons. This File must be kept for a minimum of 30 years after clinical use.

A.4.1.7.4. Availability for inspection

1. The records must be accessible at any time for inspections conducted by the competent authority. Access to the donor's identity and related data is limited to persons responsible for the TE or ORHA, but must, if necessary, be available to inspectors.

A.4.1.7.5. Traceability

1. The TE or ORHA should be able to assure the traceability of the donor.
2. The traceability requirement applies to all relevant data related to the donor, critical products and materials coming into contact with the donor.
3. Corrections, changes or amendments made to a file should be carried out according to a written change control management procedure.
4. When electronic data is affected, any critical change should be recorded and available through an audit trail.

A.5. PROCESSING

A.5.1. ACTIVITIES

A.5.1.1. Reception

1. *TEs shall ensure that all donations of human tissues and cells are subjected to tests in accordance with the requirements established and that the selection and acceptance of tissues and cells comply with them.*
2. *TEs shall ensure that human tissue and cells and associated documentation comply with the requirements established.*
3. *TEs shall verify and record the fact that the packaging of human tissue and cells received complies with the requirements established. All tissues and cells that do not comply with those provisions shall be discarded.*
4. *The acceptance or rejection of received tissues/cells shall be documented.*

⁵⁴ Commission Directive 2006/17/EC (Annex IV)

5. TEs shall ensure that human tissues and cells are correctly identified at all times. Each delivery or batch of tissues or cells shall be assigned an identifying code.

6. Tissue and cells shall be held in quarantine until such time as the requirements relating to donor testing and information have been met.⁵⁵

7. The competent authority or authorities shall ensure that the tissue and/or cell donation and procurement procedures and the reception of tissues and/or cells at the tissue establishment comply with the requirements set out.⁵⁶

A.5.1.1.1. Receipt of tissues and cells at processing centre

1. When the retrieved tissues/cells arrive at the tissue establishment, there must be documented verification that the consignment, including the transport conditions, packaging, labelling and associated documentation and samples, meet the requirements and the specifications of the receiving establishment.

2. Each establishment must ensure that the tissue and cells received are quarantined until they, along with the associated documentation, have been inspected or otherwise verified as conforming to requirements. The review of relevant donor/procurement information and thus acceptance of the donation needs to be carried out by specified/authorised persons.

3. Each tissue establishment must have a documented policy and specifications against which each consignment of tissues and cells, including samples, are verified. These must include the technical requirements and other criteria considered by the tissue establishment to be essential for the maintenance of acceptable quality. The tissue establishment must have documented procedures for the management and segregation of non-conforming consignments, or those with incomplete test results, to ensure that there is no risk of contamination of other tissues and cells being processed, preserved or stored.

4. The data that must be registered at the tissue establishment (except for donors of reproductive cells intended for partner donation) include:

- a) consent/authorisation; including the purpose(s) for which the tissues and cells may be used (i.e. therapeutic or research, or both therapeutic use and research) and any specific instructions for disposal if the tissue or cells are not used for the purpose for which consent was obtained
- b) all required records relating to the procurement and the taking of the donor history, as described in the donor documentation section

⁵⁵ Directive 2004/23/EC of the European Parliament and of the Council (Art.19)

⁵⁶ Commission Directive 2006/17/EC (Art.5)

- c) results of physical examination, of laboratory tests and of other tests (such as the autopsy report)
 - d) for allogeneic donors, a properly documented review of the complete donor evaluation against the selection criteria by an authorised and trained person
 - e) in the case of cell cultures intended for autologous use, documentation of the possibility of medicinal allergies (such as to antibiotics) of the recipient.⁵⁷
5. The TE, or ORHA and TE, should sign an agreement defining the responsibilities of each party in the transport of the tissues/cells to the tissue establishment.
6. Such transportation must be direct, without intermediate stops when possible, to ensure the safety and maintenance of the temperature conditions of the tissues and cells.

A.5.1.1.2. Verification of tissues received

1. Upon the reception of tissues and cells by the TE, the recovered material, the human samples (including blood) and the accompanying documentation must be identified and verified.
2. The documents accompanying this human material must be checked to ensure they contain all relevant information relating to the donation and sampling. During reception of the documentation, the correspondence between the packing list or shipping record is verified with the contents of the package.
3. The packaging and material obtained and the accompanying human samples should be examined to ensure that the quality of this material has not been altered in transit, checking and recording:
 - a) The identification as listed in the packing list or shipping record;
 - b) No evidence of opening or manipulation exists;
 - c) No signs of damage which may result in the deterioration of tissues or storage problems;
 - d) Number of donor;
 - e) Recovery date and time;
 - f) Tissue for transplant / research;
 - g) Source / destination;
 - h) Tissues/cells description;
 - i) Storage temperature;
 - j) Status of the tissue (e.g. quarantine).

⁵⁷ Commission Directive 2006/17/EC (Annex IV)

4. There should be a procedure in place to manage any discrepancy or non-conformity that might appear.

5. During this physical and documental reception, the tissues and cells should be stored in defined, separated and adequate location and conditions.

A.5.1.3. Identification of tissues and cells

1. Upon reception of the tissues and cells by the TE, a unique identification code should be assigned to the material recovered. This code is then completed to identify the different products and batches obtained during processing and storage.

This code should allow traceability and a formal and unambiguous identification of all tissues and cells from recovery to transplantation (including all stages of processing, storage and distribution).

2. This code will be present on the label of tissues and cells at each stage of processing and storage as well as on any documentation that relates to these tissues and cells.

The label will include, at least, the following information:

- a) Unique identification donor number (original coding);
- b) Identification of the tissue bank;
- c) Identification of the product;
- d) Batch number, if applicable.

3. A unique identifying code shall be allocated to the donor and the donated tissues and cells, during procurement or at the tissue establishment, to ensure proper identification of the donor and the traceability of all donated material. The coded data shall be entered in a register maintained for the purpose.⁵⁸

A.5.1.2. Access to the processing facilities

1. The flows of entry, transit and exit of personnel and material through the processing area and the rules of use and clothing in them should be established in order to:

- a) Minimize the risk of tissues/cells contamination
- b) Reducing the environmental bioburden
- c) Protect the staff of biohazards

⁵⁸ Commission Directive 2006/17/EC (Art.2)

2. A written procedure designed to eliminate potential contamination and / or cross contamination from personnel and materials to tissues and cells should be in place.
3. The entrance of personnel, tissue/cells and materials should be done through airlocks avoiding the direct flow of non-treated air into the cleanrooms.
4. Personnel gowning procedures should be sufficiently validated to ensure that both, gowning materials and systematic are adequate and the resulting microbial monitoring of the clothes are satisfactory.
5. The materials and tissues/cells packages should enter the facilities using a validated procedure where the cleanliness level, according to the microbial load, conforms to the destination cleanroom.
6. Personnel involved in processing should be the minimum number required for efficient planned procedures. Additional persons present in processing areas should be taken into account during risk assessment when the procedure is designed.

A.5.1.3. Processing

A.5.1.3.1. General

1. *TEs shall include in their standard operating procedures all processes that affect quality and safety and shall ensure that they are carried out under controlled conditions. TEs shall ensure that the equipment used, the working environment and process design, validation and control conditions are in compliance with the requirements established.*
2. *Any modifications to the processes used in the preparation of tissues and cells shall also meet the criteria laid down in the corresponding change control procedure.*
3. *TEs shall include in their standard operating procedures special provisions for the handling of tissues and cells to be discarded, in order to prevent the contamination of other tissues or cells, the processing environment or personnel.⁵⁹*
4. Every step of processing is performed under defined conditions to guarantee the quality of tissues and cells and the security of the staff.
5. Preparation methods include: transformation processes, the necessary equipment and material, media preparation, additional therapeutic products used and the controls performed.

⁵⁹ Directive 2004/23/EC of the European Parliament and of the Council (Art.20)

6. The requirements for personnel, premises and equipment have been developed in previous sections, as well as those on the quality control and documentation.
7. If the processing is done by a third party, a written agreement is needed between the TE and the subcontracted party.
8. The time limits between recovery, processing and storage are determined and reflected in the tissue specific GTPs. When appropriate, these maximum times from recovery (or cardiac arrest) until processing and storage are defined. The recovery, processing and storage time is written in the dossier of those tissues and cells.
9. The evaluation quality controls performed to the tissues/cells should be established and each of them should be described in written procedures.
10. The written procedures should at least include the testing method, the sample size and the accepted criteria.
11. The minimum evaluation requirements for each type of tissue/cells are described in the specific section.
12. Should in-process controls be performed in the processing area, they should be carried out ensuring that no risk is affecting the processing itself.

A.5.1.3.2. Processing methods

Processing methods should be designed to ensure both safety and biological functionality of a prepared tissue graft. Methods of processing should be validated (See validation).

A.5.1.3.3. Cross contamination

1. In order to avoid cross-contamination, the tissues from one donor should not enter at any time during processing or during storage into contact with tissues from another donor.
2. Furthermore, the grafts that must be further processed (e.g. lyophilisation, sterilization etc.) should be treated as single donors. Each tissue should have a batch number that is also mentioned in the dossier.
3. Processing techniques are critically assessed at regular intervals to ensure they always provide the desired results.
4. Non-conforming products must be identified and separated from compliant products.
5. The treatment of non-compliant products will be decided by the responsible person in charge of the tissue bank.

A.5.1.4. Quality Control

1. The evaluation quality controls performed on the tissues/cells should be established and each should be described in written procedures.
2. The written procedures should at least include the method of the test, the sample size and the accepted criteria.
3. The minimum evaluation requirements for each type of tissue/cells are described in the specific section.
4. Should in-process controls be performed in the processing area, they should be carried out ensuring that no risk affects the processing itself.

A.5.1.4.1. Microbiological control

A.5.1.4.1.1. General Principle

1. The microbiological safety of tissues and cells is based on:
 - a) Donor selection and the absence of initial contamination;
 - b) Control and monitoring of contamination during the process;
 - c) Donor environment process (Quality Control-IPC) validated methods of decontamination, sterilization or inactivation during processing of tissues and cells;
 - d) Bacteriological examinations carried out at different stages of the process.

A.5.1.4.1.2. Microbiological controls

1. Microbiological tests must focus on aerobic and anaerobic as well as fungi. If risk factors are present, it is desirable to perform additional tests for detection of mycoplasma.
2. It must be made on:
 - a) The starting or incoming tissue;
 - b) The tissue immediately prior to final packaging;
 - c) When applicable, after a stage of decontamination or sterilization (direct control or monitoring control).
3. Various procedures exist for securing microbiological control, such as decontamination by antibiotics, sterilization, or any other physicochemical methods. These procedures must be specifically adapted to the type of tissue or cells and should be validated in detail.

A.5.1.5. Packaging and labelling

- 1. Premises for the packaging of tissues/cells should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.⁶⁰*
2. TEs shall ensure that labelling, documentation and packaging conform to the requirements referred to in the tissue specific sections.
3. When applicable, reconciliation of labels edited, used and returned / rejected should be performed according to written procedures.
5. All excess labels containing quality information should be destroyed or maintained in a secure manner, when necessary, to prevent cross contamination or mix-ups.
6. Obsolete labels should be destroyed according to written procedures.
7. Printed labels should be carefully examined to ensure that information contained conforms to the corresponding tissue/cells. The results of this examination should be documented.
8. A printed label, representative of those used, should be included in the processing records.
9. Labelling and packaging operations should be designed to prevent any cross contamination or mix-ups. Simultaneous operations should be avoided or adequate measures should be taken to ensure no cross contamination or mix-ups occur.
10. Facilities where packaging or labelling operations have taken place should be inspected and documented before starting any other operation so as to guarantee that all the previous materials have been removed.

A.5.1.5.1. Packaging and labelling materials management

1. There should be written procedures describing: the receipt, identification, quarantine, sampling, examination and/or testing and release, and handling of packaging and labelling materials.
2. Records should be maintained for each shipment of labels and packaging materials showing receipt, examination, or testing, and whether accepted or rejected.
3. Containers should provide adequate protection against deterioration or contamination of the tissues/cells, that may occur during the storage and transportation conditions, and resist the preparation techniques used (e.g. sterilization). A validation study should be done.
4. Containers should be clean and sanitized to ensure that they are suitable for their intended use. These containers should not alter the quality, safety and efficacy of the tissues/cells.

⁶⁰ EU Good Manufacturing Practices Guidelines

5. Labels should be designed to adhere firmly to the container under all storage and transport conditions and the preparations techniques used. A validation study should be done.

A.5.1.5.2. Primary packaging and labelling operation

1. *The primary tissue/cell container must provide:*

- a) *type of tissues and cells, identification number or code of the tissue/cells, and lot or batch number where applicable;*
- b) *identification of the tissue establishment;*
- c) *expiry date;*
- d) *in the case of autologous donation, this has to be specified (for autologous use only) and the donor/recipient has to be identified;*
- e) *in the case of directed donations - the label must identify the intended recipient;*
- f) *when tissues and cells are known to be positive for a relevant infectious disease marker, it must be marked as: BIOLOGICAL HAZARD;*
- g) *If applicable, the fluid in which the tissue is preserved.*

2. *If any of the information under points (d) and (e) above cannot be included on the primary container label, it must be provided on a separate sheet accompanying the primary container. This sheet must be packaged with the primary container in a manner that ensures that they remain together.*

3. *The following information must be provided either on the label or in accompanying documentation:*

- a) *description (definition) and, if relevant, dimensions of the tissue or cell product;*
- b) *morphology and functional data where relevant;*
- c) *date of distribution of the tissue/cells;*
- d) *biological determinations carried out on the donor and results;*
- e) *storage recommendations;*
- f) *instructions for opening the container, package, and any required manipulation/reconstitution;*
- g) *expiry dates after opening/manipulation.*
- h) *instructions for reporting serious adverse reactions and/or events as set out in Biovigilance B.6;*
- i) *presence of potential harmful residues (e.g. antibiotics, ethylene oxide etc.).⁶¹*

A.5.1.5.3. Secondary packaging and labelling operation

⁶¹ Commission Directive 2006/86/EC (Annex II)

1. For transport, the primary container must be placed in a shipping container that must be labelled with at least the following information:

- a) Identification of the originating tissue establishment, including an address and phone number;*
- b) Identification of the organisation responsible for human application of destination, including address and phone number;*
- c) A statement that the package contains human tissue/cells and HANDLE WITH CARE;*
- d) Where living cells are required for the function of the graft, such as stem cells gametes and embryos, the following must be added: 'DO NOT IRRADIATE';*
- e) Recommended transport conditions (e.g. keep cool, in upright position, etc.);*
- f) Safety instructions/method of cooling (when applicable);*
- g) Expiry date;⁶²*
- h) Identification of the tissue, donor identification number, type of tissue or cells, and batch number if applicable;*
- i) The words 'AUTOLOGOUS USE' and the recipient's identification in case of autologous donation;*
- j) The recipient's identification in case of directed donation.*

A.5.1.6. Documentation and release in distribution

A.5.1.6.1. General

- 1. There must be a system in place that results in clearly defined and effective documentation, correct records and registers and authorised Standard Operating Procedures (SOPs), for the activities for which accreditation/designation/ authorisation/licensing is sought. Documents must be regularly reviewed and must conform to the standards laid down in this text. The system must ensure that work performed is standardised, and that all steps are traceable; i.e. coding, donor eligibility, procurement, processing, preservation, storage, transport, distribution or disposal, including aspects relating to quality control and quality assurance.*
- 2. For every critical activity, the materials, equipment and personnel involved must be identified and documented.*
- 3. In the TEs all changes to documents must be reviewed, dated, approved, documented and implemented promptly by authorised personnel.*
- 4. A document control procedure must be established to provide for the history of document reviews and changes and to ensure that only current versions of documents are in use.*
- 5. Records must be shown to be reliable and a true representation of the results.*

⁶² Commission Directive 2006/86/EC (Annex II)

6. Records must be legible and indelible and may be handwritten or transferred to another validated system, such as a computer or microfilm.⁶³

7. A validation study should be performed to show the effectiveness of the processing procedures. Procedures should be written identifying the key aspects to be considered and they should include but not limited to:

- a) Access to the processing area;
- b) Gowning requirements;
- c) Measures to prevent contamination from the facilities, operators and materials;
- d) Cleanrooms and equipment qualification and calibration;
- e) Microbial and airborne routine monitoring;
- f) Materials used during processing;
- g) Critical processing steps;
- h) Tissues/cells specifications;
- i) Quality controls, analytical methods and acceptance criteria;
- j) Sampling plan;
- k) Packaging and labelling materials, literature and operations;
- l) Transport validation (include time period from initial packaging to destination arrival).

7. Generally, it is considered as acceptable that three consecutive processes within the finally agreed parameters would constitute a validation of the process.

A.5.1.6.2. Release

1. The items indicated in the Processing File Contents (see A.5.1.6.3) should be required for the release or rejection of the tissues/cells and thus should be documented. The processing dossier should include the contents shown in the Processing File Contents section.

2. The responsible person for Processing should make and sign a statement, which specifies the fulfilment of all ethical and legal requirements, releasing the tissue/cells for transplant or investigation. When any evaluation is pending at the moment of the release, the statement should mention specifically that it is a partial release and that the results and final release will be conveyed in writing, as soon as technically possible.

A.5.1.6.3. Processing File Contents

1. The Processing File will contain at least:

⁶³ Commission Directive 2006/86/EC (Annex I)

- a) The Recovery File and/or release statement of Recovery Responsible Person;
- b) Type of tissues and cells processed and / or stored;
- c) Quantitative and qualitative description of tissues and cells processed, preserved and / or stored;
- d) Date and time of each stage of processing and storage, the identification of persons responsible for each step and the identifying media and related products used (Batch Number and expiry date);
- e) Status of tissues and cells at all stages of processing and storage (i.e. quarantine, released for therapeutic use, in vitro research, etc.);
- f) Use of antibiotics, antibiotic composition; incubation period. if applicable;
- g) Type and amount of media used;
- h) Procedures and records concerning the processing of tissues and cells, if applicable;
- i) Processing data (preparation, culture technique, incubation, treatment chemicals);
- j) Data on the conservation (i.e cryopreservation, tracing the curve of cooling, glycerolisation, lyophilisation, etc.);
- k) Data on techniques of decontamination, sterilization and viral inactivation;
- l) Results of specific quality test depending on tissues and cells type (e.g. HLA, histology, radiology results, cell viability or tissue, etc.);
- m) Procedures and records concerning the preservation of tissues and cells, if applicable;
- n) Date and time of storage;
- o) Method of storage;
- p) Storage temperature;
- q) Expiring date;
- r) Identification of tissues and cells: Donor identification code (ID) + product code.

Access to registers and data must be restricted to persons authorised. This File must be kept for a minimum of 30 years after clinical use.

A.5.1.6.4. Availability for inspection

1. The records must be accessible at any time for inspections conducted by the competent authority. Donor identity and data related to it will be restricted to the TE but must, if necessary, be available for inspectors.

A.5.1.6.5. Traceability

1. The TE must guarantee that the establishment, institution or surgeon to whom the tissue or cells are delivered is able to ensure traceability: it should be embodied in a document or written agreement with explicit traceability conditions.
2. The dossier must ensure the traceability of tissues and cells processed by the bank.

3. Traceability must be ensured from donor to recipient (or until the removal of tissues or cells concerned) and vice versa. The traceability of the donor up to distribution is the responsibility of the TE, while traceability from reception of the tissue or cells up to its use is the responsibility of the institution that receives it.

4. The establishment receiving the tissues and cells should record:

- a) Identification of the human material;
- b) TEs providing the material;
- c) The final destination (distribution, delivery and implementation in a recipient or disposal);
- d) Identification of recipient;
- e) The date of implantation.

5. The traceability requirements apply to all relevant data related to products and materials that may come into contact with these tissues and cells.

7. Corrections, changes or amendments made to a file should be carried out according to a written change control management procedure.

8. When electronic data is affected, any critical change should be recorded and available through an audit trail.

9. *TEs shall have effective and accurate systems to uniquely identify and label cells/tissues received and distributed.*

11. A single European identifying code shall be allocated to all donated material at the tissue establishment, to ensure proper identification of the donor and the traceability of all donated material and to provide information on the main characteristics and properties of tissues and cells.⁶⁴ The code shall incorporate at least:

- a) *Donation identification;*
 - i. *Unique ID number*
 - ii. *Identification of the tissue establishment*
- b) *Product identification;*
 - i. *Product code (basic nomenclature)*
 - ii. *Split number (if applicable)*
 - iii. *Expiry date.⁶⁵*

⁶⁴ Commission Directive 2006/86/EC (Art.10)

⁶⁵ Commission Directive 2006/86/EC (Annex VII)

A.6. STORAGE AND DISTRIBUTION

A.6.1. GENERAL

1. When the activities for which the accreditation/ designation/ authorisation/ licensing is sought include storage and release of tissues and cells, the authorised TE procedures must comply with the following criteria:

- a) Maximum storage time must be specified for each type of storage condition. The selected period must, among other things, reflect possible deterioration of the required tissue and cell properties.*
- b) There must be a system of inventory hold for tissues and/or cells to ensure that they cannot be released until all requirements laid down in this Directive have been satisfied. There must be a standard operating procedure that details the circumstances, responsibilities and procedures for the release of tissues and cells for distribution.*
- c) A system for identification of tissues and cells throughout any phase of processing in the tissue establishment must clearly distinguish released from non-released (quarantined) and discarded products.*
- d) Records must demonstrate that before tissues and cells are released all appropriate specifications are met, in particular all current declaration forms, relevant medical records, processing records and test results have been verified according to a written procedure by a person authorised for this task by the responsible person. If a computer is used to release results from the laboratory, an audit trail should indicate who was responsible for their release.*
- e) A documented risk assessment approved by the responsible person must be undertaken to determine the fate of all stored tissues and cells following the introduction of any new donor selection or testing criterion or any significantly modified processing step that enhances safety or quality.⁶⁶*

2. TE shall ensure that all procedures associated with the storage of tissues and cells are documented in the standard operating procedures and that the storage conditions comply with the requirements referred to in this text.

3. TE shall ensure that all storage processes are carried out under controlled conditions.

4. TE shall establish and apply procedures for the control of packaging and storage areas, in order to prevent any situation arising that might adversely affect the functioning or integrity of tissues and cells.

5. Tissues shall not be distributed until all the requirements laid down in Directive 2004/23/EC have been met⁶⁷.

⁶⁶ Commission Directive 2006/86/EC (Annex II)

⁶⁷ Directive 2004/23/EC of the European Parliament and of the Council (Art. 21)

6. Each tissue bank should establish validated temperature-range limits and storage times for each tissue product, depending on its processing, packaging and intended use.
7. All human tissue prior to determination of suitability must be under *Quarantine*. Quarantined tissues should be physically separated and visibly different from released tissues, by labelling or packaging. Where a donor sample tests positive or reactive for an infectious marker, the tissue should immediately be removed from the quarantine inventory.
8. Where quarantined tissue is shipped for processing or storage, it should be accompanied by records ensuring identification of the donor and indicating that the tissue has not been determined suitable for transplantation. Tissue determined to be unsuitable for transplantation and intended for release for other purposes should be identified accordingly.
9. Quarantine records for tissue quarantined post-release should indicate the reason for quarantine and the final disposition of the tissue. Release dates or disposal dates should be indicated as well.
10. Policies and procedures should be developed for the emergency transfer of tissue to designated alternative storage facilities, and for alternative monitoring methods, in the event of mechanical failure or loss of coolant. These should include specification of Tolerance Limits or temperatures and time limits after which the initiation of the emergency transfer is required. Actions to be taken when limits have been exceeded should also be specified in the relevant SOP.

A.6.2. DISTRIBUTION

1. When the activities for which the accreditation, designation, authorisation, licensing is sought include distribution of tissues and cells, the authorised TE procedures must comply with the following criteria:

- a) *Critical transport conditions, such as temperature and time limit must be defined to maintain the required tissue and cell properties.*
- b) *The container/package must be secure and ensure that the tissue and cells are maintained in the specified conditions. All containers and packages need to be validated as fit for purpose.*

- c) Where distribution is carried out by a contracted third party, a documented agreement must be in place to ensure that the required conditions are maintained.⁶⁸
2. The choice of transport mode is made according to general regulations governing transportation. The transportation of tissues is carried out following a validated procedure according to the safety and preservation criteria for each tissue type. These conditions are reflected in the tissue specific GTPs.
 3. If tissue to be distributed requires specific environmental conditions other than ambient temperature, the capability of the transport container to maintain the required environmental conditions should be demonstrated and documented in a validation study. The length of time that these conditions can be maintained by the transport container, assuming normal handling, should also be determined and documented.
 4. The place, date and time of departure and arrival, and the identity of the person receiving the tissues should be recorded and kept in the TE or ORHA.
 5. If the transport is sub-contracted, a written agreement must be signed between the transporter and the TE which describes what should happen when tissue is damaged or lost during transportation.
 6. Any transportation must be accompanied by a transport document that will be attached to the dossier.

A.6.3. IMPORT AND EXPORT

Although the number of transplantations each year has grown rapidly over the past two decades, the demand for transplantation using human cells, tissues and organs has increased significantly, resulting in a continuing shortage of human material, particularly organs. Few countries are near to being self-sufficient in the provision of cells, tissues and organs for transplantation.

Efforts should be made to increase the donation of human material, to achieve national self-sufficiency, and to prevent ‘transplant tourism’ and the ‘trafficking’ of human cells, tissues and organs.

Success in increasing donations of cells, tissues and organs in order to meet global needs depends on public acceptance of safe, legal donation and transplantation, together with public awareness of the dangers of commercial trade and ‘trafficking’.

⁶⁸ Commission Directive 2006/86/EC (Annex II)

With the growing global circulation of transplantable material, traceability is a major concern for transplant professionals and surveillance systems. There would be significant advantages in developing a common basis for a global system for coding transplantable material, especially cells and tissues. The use of a global coding system could also offer benefits in combating commercial trade.

The allocation of organs, cells and tissues should be guided by clinical criteria and ethical norms, not financial or other considerations. Allocation rules, defined by appropriately constituted committees, should be equitable, externally justified, and transparent.

- 1. Member States shall take all necessary measures to ensure that all imports of tissues and cells from third countries are undertaken by tissue establishments accredited, designated, authorised or licensed for the purpose of those activities, and that imported tissues and cells can be traced from the donor to the recipient and vice versa in accordance with the procedures referred to in Article 8. Member States and tissue establishments that receive such imports from third countries shall ensure that they meet standards of quality and safety equivalent to the ones laid down in this Directive.*
- 2. Member States shall take all necessary measures to ensure that all exports of tissues and cells to third countries are undertaken by tissue establishments accredited, designated, authorised or licensed for the purpose of those activities. Those Member States that send such exports to third countries shall ensure that the exports comply with the requirements of this Directive.*
- 3. (a) The import or export of tissues and cells referred to in Article 6(5) may be authorised directly by the competent authority or authorities.*
(b) In case of emergency, the import or export of certain tissues and cells may be authorised directly by the competent authority or authorities.
(c) The competent authority or authorities shall take all necessary measures to ensure that imports and exports of tissues and cells referred to in subparagraphs (a) and (b) meet quality and safety standards equivalent to those laid down in this Directive.

4. *The procedures for verifying the equivalent standards of quality and safety in accordance with paragraph 1 shall be established by the Commission, in accordance with the procedure referred to in Article 29(2).*⁶⁹
5. The tissues and cells Directives (EUTCD) (transposed into EU Member State laws, regulations and standards) should ensure that, within the EU, human tissues and cells, whatever their intended use, are of comparable safety and quality even if procured in another Member State, particularly in order to prevent the transmission of diseases and therefore to protect the health of EU citizens who receive human tissue cells and treatments.
6. In addition, wherever tissues and cells for human application enter or leave the EU, they should have met the standards or equivalent to those laid down in the EU Member State laws, regulations and standards, which may be more stringent than the EUTCD.
7. The terms ‘import’ and ‘export’ relate to the exchange of goods (human tissues in this case) respectively from or to countries outside of the EU.
8. The transit of tissues (the import of tissues only for transfer to another EU Member State or for export to a non-EU country) should be considered as an import followed, possibly after a processing and/or storage step, by a transfer or an export.
9. A fair balance in the exchange of human tissue must be sought in order not to undermine the legitimate public health interests in the importing and exporting countries.
10. The import and export of tissues should not be guided by financial considerations (i.e profit-maximizing practices).
11. TEs wishing to import or export tissues should be able to demonstrate that the purposes for which they wish to import or export such material cannot be adequately met by comparable material available from sources within those countries, or is for a particular justifiable purpose. TEs should be able to document the need for importing or exporting in terms of accessibility, quality, timeliness of supply, risk of infection, or quality of service. Such documentation should be available for inspection by the CA.
12. Imports and exports of tissues may only be undertaken by TEs accredited, designated, authorised or licensed for the purpose of those activities.

⁶⁹ Directive 2004/23/EC of the European Parliament and of the Council (Art.9)

13. The transport conditions should maintain the quality and safety of the tissues.
14. TEs that import and export tissues should ensure that they comply with the requirements of:
 - a) The relevant national laws, regulations and standards of the importing and exporting countries.
 - b) The WHO Guiding Principles on Human Cell, Tissue and Organ Transplantation (provide an orderly, ethical and acceptable framework for the acquisition and transplantation of human cells, tissues and organs for therapeutic purposes).
 - c) ⁷⁰The Declaration of Helsinki ⁷¹(reinforces consent and ethics issues)
15. The importing or exporting TE should have in place procedures for verifying that the tissues comply with the above-mentioned requirements. It is recommended that TEs perform audits of the TEs from and to which they regularly import or export considerable amounts of tissues. Such an audit should include a review of compliance with the above-mentioned requirements.
16. Approval of imported tissues and approval for exportation of tissues are done under the responsibility of the responsible person of the importing or exporting TE.
17. The terms of import and export of tissues must be described in a document detailing the responsibilities and commitments of each party.
18. Important points of concern are:

Source

- a) Importing TEs should satisfy themselves, with due assurance from their collaborators abroad, that any material intended for import is sourced consistently with the legal and ethical requirements in both the importing and exporting countries;
- b) If the importing TE cannot ensure that ethical standards have been put in place, the tissues should not be imported.

Consent

- a) Importing TEs should satisfy themselves that, in the countries from which they seek to import tissue, the gaining of consent for the purpose to which the tissue is subsequently put is part of the process by which the material is obtained

⁷⁰ WHO. Human organ and tissue transplantation. Report by the Secretariat. Sixty-Second World Health Assembly. March 26, 2009.

⁷¹ World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964;

(including providing donors, their legal representatives or their family with the information that their tissues may be exported for use abroad).

- b) The importing TE should have in place reliable procedures which clearly set out the evidence indicating how informed consent was obtained, including safeguarding the confidentiality of all information relating to consent.

Import/export register

- a) Relevant data concerning the import and export of tissues should be retained in a safe place in the TE and should be available for inspection by the CA. This import/export register should include details of the reason why the decision was made to import or export the tissues, of when the tissues were imported or exported and where from or to, the uses to which they were put, when the tissues were transferred elsewhere and to whom.

Traceability

- a) Imported tissues must be traceable from the donor to the recipient and vice versa. This traceability should also apply to all relevant data relating to products and materials coming into contact with these tissues.
- b) A unique code must be assigned to each donation and to each of the products associated with it.
- c) All imported and exported tissues must be uniquely identified with a label that contains the information or references allowing a link to the information regarding tissue procurement, reception, processing, storage and distribution or disposal. The label should at all times mention the name and address of the facility where the tissue was procured and the TE that performed the procurement.
- d) TEs should keep the data necessary to ensure traceability at all stages. Data required for full traceability (see Annex VI of Commission Directive 2006/86/EC of 24 October 2006), including the import/export register, should be kept for a minimum of 30 years after clinical use or the expiry date, in an appropriate and readable storage medium acceptable to the CA. Data storage may also be in electronic form.

A.6.4. DOCUMENTATION AND RELEASE

A.6.4.1. General

1. The TE or ORHA must develop a system to maintain a record of each step of donation, donor selection, collection, control, preparation, storage and distribution of tissues and cells. The decision to release (validation for human use) is taken on the basis of data contained in this dossier.
2. The records and documents must be completed in a legibly and indelibly manner.
3. The dossier and any other documentation can also be saved on a reliable system such as a digital or microfilm system. When data is managed by tissue bank personnel, a declaration must be made to the Competent Institution for personal data protection according to current regulations.
4. The recording of relevant data in the dossier must allow identification of the author and the date of these entries.
5. Data security and confidentiality must be guaranteed.

A.6.4.2. Release

1. The items indicated in the Storing and Distribution File Contents should be required for the release or rejection of the tissues / cells and thus should be documented. The tissue / cells recovered dossier should include the contents showed in the Recovery File Contents section.

A.6.4.3. Storing and Distribution File Contents

1. The organisation performing the procurement must prepare a procurement report, which is passed on to the tissue establishment. This report must contain at least:
 - a) Reception records for tissues/cells;
 - b) Release statements of the corresponding responsible persons;
 - c) Conditions under which the tissues or cells are kept (conditions and time);
 - d) Shipping records with the name and address of the tissue establishment to receive the cells/tissues;
 - e) Date of issuance or distribution or destruction.
2. The tissue bank sets up a procedure to ensure the registration of the following information to guarantee traceability of tissues and cells and to report incidents or serious adverse reactions;
 - a) Identification of the recipient (name and date of birth);

- b) Identification of the surgeon in charge of implantation;
- c) Place and date of implantation;
- d) Clinical follow-up (initial results, complications and remarks);
- e) Description of the tissues and cells (such as quantitative data, morphological data, functional data);
- f) Recommendations of interim storage, if any;
- g) Instructions for use (such as opening instructions, thawing and / or reconstitution, handling, etc.);
- h) Conditions and the maximum period of storage after deconditioning. This dossier also includes a form to be completed by the surgeon after implantation and be returned to the TE. It will contain relevant information related to possible SAEs and/or SARs that may occur during implantation.

Access to registers and data must be restricted to persons authorised. This file must be kept for a minimum of 30 years after clinical use.

A.6.4.4. Availability for inspection

The records must be accessible at any times for inspections conducted by the Competent Authority. Access to the donor's identity and data related is limited to persons responsible for the TE or ORHA, but must, if necessary, be allowed to inspectors.

A.6.4.5. Traceability

1. The TE or ORHA should be able to assure the traceability of the donor.
2. The traceability requirement applies to all relevant data related to the donor, critical products and materials coming into contact with the donor.
3. Corrections, changes or amendments made to a file should be carried out according to a written change control management procedure.
4. When electronic data is affected any critical change should be recorded and available through an audit trail.

A.7. QUALITY MANAGEMENT

A.7.1. QUALITY ASSURANCE

A.7.1.1. General

1. Member States shall take all necessary measures to ensure that each tissue establishment puts in place and updates a quality system based on the principles of good practice.⁷²

2. Any person involved in the process is responsible for quality. The management must have a systematic approach to quality assurance and to the implementation and maintenance of quality assurance system.

3. The quality system includes quality assurance, quality control and continuous improvement of quality, personnel, facilities, equipment, documentation, recovery, donor selection, testing, preservation, storage, distribution, the recall of tissues and cells, the external and internal auditing, contract management, non-compliance and self-inspection.

4. The quality assurance system guarantees that all critical procedures are described in SOP's and are performed according to them. The effectiveness of the system is periodically evaluated by the management.

5. The quality system appropriate for the processing of tissues and cells should ensure that:

- a) Tissues and cells are designed and developed in a way that takes account of the requirements of good tissue practices (GTP);
- b) Processing and operations are clearly specified and good tissue practice adopted;
- c) Managerial responsibilities are clearly specified;
- d) Arrangements are made for the processing, supply and use of the correct starting and packaging materials;
- e) All necessary controls on intermediate phases and in-process controls, and validations are carried out;
- f) The finished tissues and cells are correctly processed and checked, according to the defined procedures;
- g) Tissues and cells are not sold or supplied before the responsible person, or a person authorized by a responsible person has certified that each tissue / cells have been processed and controlled in accordance with the requirements of the Establishment Authorisation and any other regulations relevant to the processing, control and release of tissues and cells;
- h) Satisfactory arrangements exist to ensure, as far as possible, that the tissues and cells are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life;
- i) There is a procedure for self-inspection and/or quality audit which regularly appraises the effectiveness and applicability of the quality assurance system.

⁷²Directive 2004/23/EC of the European Parliament and of the Council (Art.16)

A.7.1.2. Documentation

1. *There must be a system in place that results in clearly defined and effective documentation, correct records and registers and authorised SOPs, for the activities for which accreditation/designation/ authorisation/licensing is sought. Documents must be regularly reviewed and must conform to the standards laid down in this text. The system must ensure that work performed is standardised, and that all steps are traceable; i.e. coding, donor eligibility, procurement, processing, preservation, storage, transport, distribution or disposal, including aspects relating to quality control and quality assurance.*
2. *For every critical activity, the materials, equipment and personnel involved must be identified and documented.*
3. *In the TEs all changes to documents must be reviewed, dated, approved, documented and implemented promptly by authorised personnel.*
4. *A document control procedure must be established to provide for the history of document reviews and changes and to ensure that only current versions of documents are in use.*
5. *Records must be shown to be reliable and a true representation of the results.*
6. *Records must be legible and indelible and may be handwritten or transferred to another validated system, such as a computer or microfilm.⁷³*
7. The documentation system must assure that:
 - a) All processing operations are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently process tissues and cells of the required quality and complying with their specifications;
 - b) Critical steps of processing and significant changes to the processes are validated;
 - c) All necessary facilities for GTP are provided including:
 - i. Appropriately qualified and trained personnel;
 - ii. Adequate premises and space;
 - iii. Suitable equipment and services;
 - iv. Correct materials, containers and labels;
 - v. Approved procedures and instructions;
 - vi. Suitable storage and transport
 - d) Instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;
 - e) Operators are trained to carry out procedures correctly;

⁷³ Commission Directive 2006/86/EC (Annex I)

- f) Records are made, manually and/or by recording instruments, during processing which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the tissues and cells was as expected. Any significant deviations are fully recorded and investigated;
 - g) Records of processing including distribution, which enable the complete history of a tissue/cells (see traceability section) to be traced, are retained in a comprehensible and accessible form;
 - h) The distribution of the tissues and cells minimises any risk to their quality;
 - i) A system is available to recall any tissue / cells from sale or supply;
 - j) Complaints about supplied tissues and cells are examined, the causes of quality defects investigated and appropriate measures taken in respect to prevent the reoccurrence of the quality defects of tissues and cells.
8. The TE must maintain a registry of SOPs, in which every activity (including donation, donor screening, collection, codification, preparation, laboratory testing, storage, transmission and distribution) is clearly defined and described. It will include aspects related to quality control and quality assurance. Each of these procedures will be reviewed and monitored regularly and adjusted if necessary. All revisions are documented, dated and signed for approval.

Keeping records of previous versions should help to ensure that only the most recent version is being used. Copies of the latest version should be available to the staff of the TE.

9. TEs should take all necessary measures to ensure that the quality system includes at least the following documentation:

- a) Standard operating procedures;
- b) Guidelines;
- c) Training and reference manuals;
- d) Reporting forms;
- e) Donor records;
- f) Information on the final destination of tissues or cells.

This should be described in a Quality Manual.

10. TEs should take all necessary measures to ensure that the documentation is available for inspection by the competent authority or authorities.

11. Access to registers and data must be restricted to persons authorised by the responsible person, and to the competent authority for the purpose of inspection and control measures.

12. All the records must be clear and readable, protected from unauthorised amendment and retained and readily retrieved in this condition throughout their specified retention period in compliance with data protection legislation.⁷⁴

13. Donor records required for full traceability must be kept for a minimum of 30 years after clinical use.

A.7.1.3. Non-compliance management

1. Deviations from the required standards of quality and safety must lead to documented investigations, which include a decision on possible corrective and preventive actions. The fate of non-conforming tissues and cells must be decided in accordance with written procedures supervised by the responsible person and recorded. All affected tissues and cells must be identified and accounted for.

2. Corrective actions must be documented, initiated and completed in a timely and effective manner. Preventive and corrective actions should be assessed for effectiveness after implementation.⁷⁵

A.7.1.4. Internal Audit

1. An audit system must be in place for the activities for which accreditation /designation/authorisation/licensing is sought. Trained and competent persons must conduct the audit in an independent way, at least every two years, in order to verify compliance with the approved protocols and the regulatory requirements. Findings and corrective actions must be documented.⁷⁶

It is recommended that the internal audit plan be created on risk assessment basis.

2. An external audit conducted by a competent person independent of the bank would be desirable. Both, the findings and corrective actions must be documented.

3. Personnel matters, premises, equipment, documentation, processing, quality control, distribution of the tissues and cells, arrangements for dealing with complaints and recalls, and self-inspection, should be examined at intervals following a pre-arranged programme in order to verify their conformity with the principles of Quality Assurance.⁷⁷

⁷⁴ Commission Directive 2006/17/EC (Annex IV)

⁷⁵ Commission Directive 2006/86/EC (Annex I)

⁷⁶ Commission Directive 2006/86/EC (Annex I)

⁷⁷ EU Good Manufacturing Practices Guidelines

4. Member States shall also ensure that appropriate control measures are in place for the procurement of human tissues and cells.
5. Such inspections and control measures shall be carried out by officials representing the competent authority who shall be empowered to:

 - a) Inspect TEs and the facilities of any third parties;
 - b) Evaluate and verify the procedures and the activities carried out in TEs and the facilities of third parties that are relevant;
 - c) Examine any documents or other records relating to the requirements of this text.
6. The competent authority or authorities shall organise inspections and carry out control measures as appropriate whenever there is any serious adverse reaction or serious adverse event. In addition, such an inspection shall be organised and control measures shall be carried out at the duly justified request of the competent authority or authorities in another Member State in any such case.
7. Member States shall, upon the request of another Member State or the Commission, provide information on the results of inspections and control measures carried out in relation to the requirements of this text.⁷⁸
8. The use of the checklist tool coming from the EQSTB project is recommended (see G.4. EQSTB CHECKLIST)

A.7.1.5. Product Quality Review/Process Quality Review

1. The tissue establishment should have processes in place for review of the performance of the quality management system to ensure continuous and systematic improvement.⁷⁹
2. Regular periodic quality reviews of all tissues and cells, including export ones, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished tissues and cells to highlight any trends and to identify tissues/cells and process improvements.⁸⁰
3. Such reviews should normally be conducted and documented annually; taking into account previous reviews, and should include at least the items indicated in those paragraphs.
4. The results of this review should be evaluated and an assessment should be made whether corrective and preventive action or any revalidation should be undertaken. Reasons for such

⁷⁸ Directive 2004/23/EC of the European Parliament and of the Council (Art 7)

⁷⁹ Commission Directive 2006/86/EC (Annex I)

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corrective actions should be documented. Agreed corrective and preventive actions should be completed in a timely and effective manner. There should be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self-inspection.

5. *Quality reviews may be grouped by tissues/cells type, where scientifically justified.⁸¹*

A.7.1.5.1. Donor screening

The donor screening process should be evaluated regularly in order to assess its consistency. The Process Quality Review (PQR) will consider whether the procedures are effective.

At least the following issues are suggested to be taken into account:

- a) Previous reviews;
- b) A review of death cases in the common generator centres, number of cases detected in an adequate period of time and cases not detected;
- c) Review of traceability lost cases;
- d) Review of donor contamination or deterioration during maintenance;
- e) Review of familiar and judicial negatives;
- f) Review of non compliance of the consent scope;
- g) Review of donor evaluation and exclusion criteria checklist;
- h) Review of all the critical deviations and non-conformities and their investigations;
- i) Review of any change established in the process;
- j) Review of the key performance indicators.

A.7.1.5.2. Recovery

The recovery process should be evaluated regularly in order to assess its consistency. This PQR will consider whether the procedures are effective and adequate.

At least the following issues are suggested to be taken into account:

- a) Previous reviews;
- b) Review of facilities and materials microbiological monitoring results;
- c) Review of tissues and/or cells contamination cases caused by operators, materials or facilities;
- d) Review of tissues and/or cells contamination cases caused by the own donor;
- e) Review of cross contamination when applicable;
- f) Review of critical quality controls;

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- g) Review of all the critical deviations and non-conformities and their investigations;
- h) Review of any change established in the process;
- i) Review of the process validation studies;
- j) Review of the facilities qualification and equipment calibrations;
- k) Review of the key performance indicators.

A.7.1.5.3. Processing

The processing processes should be evaluated regularly in order to assess their consistency on the obtaining of quality tissues and cells. This product quality review will consider whether the procedures are effective.

At least the following issues are suggested to be taken into account:

- a) Previous reviews;
- b) Deviations and non-conformities observed during reception activities;
- c) Review of starting materials including packaging materials used in the tissues/cells, especially those from new sources;
- d) Review of critical quality control tests;
- e) Review of all tissues/cells that failed to meet established specification(s) and their investigation;
- f) Review of all significant deviations or non-conformances from the processing procedures, their related investigations, and the effectiveness of resultant corrective and preventive actions taken;
- g) Review of all changes carried out to the processes or analytical methods;
- h) Review of the results of the stability monitoring programme and any adverse trends;
- i) Review of microbial and airborne results of routine monitoring results;
- j) Review of all quality-related returns, complaints and recalls and the investigations performed at the time;
- k) Review of patient follow-up information;
- l) Review of adequacy of any other previous product process or equipment corrective actions;
- m) Calibration and qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc.;
- n) Review of the process validation studies;
- o) Review of gowning requirements;
- p) Review of cleanrooms and equipment corrective maintenance activities needed;
- q) Review of any contractual arrangements as defined critical third party agreements section to ensure that they are up to date;
- r) Review of the deviations detected during packaging and labelling operations;
- s) Review of the deviations detected during storage or transport;

- t) Review of the key performance indicators.
9. Quality reviews may be grouped by tissue/cells type where scientifically justified.

A.7.1.5.4. Distribution

The distribution processes should be evaluated regularly in order to assess their consistency on maintaining the quality of tissues and cells. This process quality review will consider whether the procedures are effective.

The following issues are suggested to be taken into account:

- a) Previous reviews;
- b) Deviations and non-conformities observed during shipment activities;
- c) Review of packaging materials used in the tissues/cells, especially those from new sources;
- d) Review of all tissues/cells that suffered any damage during transport because a failure of the shipping system and their investigation;
- e) Review of all significant deviations or non-conformances from the distribution procedures, their related investigations, and the effectiveness of resultant corrective and preventive actions taken;
- f) Review of all changes carried out to the distribution processes;
- g) Review of the shipping system validation studies;
- h) Review of any contractual arrangements as defined in Critical third party agreements section to ensure that they are up to date;
- i) Review of the deviations detected during storage;
- j) Review of the SAE and SAR that might have occurred;
- k) Review of the key performance indicators.

10. Quality reviews may be grouped by tissue / cells type where scientifically justified.

11. It is recommended to extend the quality review to a more general management review including other processes of the organization (e.g. finances, purchasing, personnel, ICT).

A.7.1.6. Recalls

1. *There must be personnel authorised within the tissue establishment to assess the need for recall and to initiate and coordinate the necessary actions.*
2. *An effective recall procedure must be in place, including a description of the responsibilities and actions to be taken. This must include notification to the competent authority.*

3. Where tissue that has been released is subsequently deemed to have been unsuitable for transplantation, it must be recalled. *Actions must be taken within pre-defined periods of time and must include tracing all relevant tissues. Any donor who might have contributed to causing a reaction in the recipient must be traced to retrieve available tissues and cells from that donor, as well as to notify hospitals and recipients of tissues and cells, or organs, procured from the same donor in the event that they might have been put at risk.*
4. *A documented system must be in place for the handling of returned products including criteria for their acceptance into the inventory, if applicable.⁸²*
5. *There should be established written procedures, regularly checked and updated when necessary, in order to organise any recall activity.*
6. *Recall operations should be capable of being initiated promptly and at any time.*
7. *All parties to which tissues/cells may have been distributed should be informed promptly if tissues / cells are intended to be recalled because they are, or are suspected of being defective.*
8. *The distribution records should be readily available in the event of a recall including those for exported tissues/cells.*
9. *Recalled tissues / cells should be identified and stored separately in a secure area while awaiting a decision on their fate.⁸³ If the tissues can not be used for human application after recall, this shall be clearly marked and rejected. However, those tissues can be used for other purposes;*
- a) For preparation techniques of some tissues (p.exe control tissue cryopreservation)
 - b) For quality control of tissue affected in the tissue bank; it is then included in the record of the rejected tissue;
 - c) For medical research. The donor's consent is required for this specific purpose and the research protocol must be approved by an ethics committee.
11. *The progress of the recall process should be recorded and a final report issued, including reconciliation between the delivered and recovered quantities of the tissues/cells.*
12. *The effectiveness of the arrangements for recalls should be evaluated regularly⁸⁴*

A.7.1.7. Complaints and returns

1. *There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.*

⁸² Commission Directive 2006/86/EC (Annex II)

⁸³ EU Good Manufacturing Practices Guidelines

⁸⁴ EU Good Manufacturing Practices Guidelines

2. Any complaint concerning a tissue/cells defect should be recorded with all the original details and thoroughly investigated.
3. If a tissue/cells defect is discovered or suspected, consideration should be given to checking other batches in order to determine whether they are also affected.
4. All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding file.⁸⁵
5. Complaint records should be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of distributed tissues/cells and to ensure that corrective and preventive actions are implemented and are effective.
6. There should be a written policy that defines the circumstances in which returned tissue might be replaced in the inventory for subsequent re-distribution. In this case, it should be confirmed that all criteria for quality and safety have been maintained, e.g. temperature control and package integrity.⁸⁶

A.7.2. *QUALITY CONTROL*

A.7.2.1. *General*

1. Quality control should be extended to sampling, specifications and testing, as well as the organisation, documentation and release procedures that ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor tissues and cells released for sale or supply, until their quality has been judged to be satisfactory.
2. The basic requirements of quality control are that:
 - a) Adequate facilities, trained personnel and approved procedures are available for sampling, inspecting and testing of starting materials, packaging materials, tissues and cells in all their phases, and where appropriate for monitoring environmental conditions;
 - b) Samples of starting materials, packaging materials, tissues and cells in all their phases are taken by personnel and by methods approved by quality control;
 - c) Test methods are validated;
 - d) Manufacturer's Certificate of Analysis may be accepted as adequate release criteria for commercial materials on the basis of risk assessment. Self-made starting materials must be tested;

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- e) Records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated;
- f) Records are made of the results of inspection and that testing of materials, tissues and cells in all their phases are formally assessed against specification. Tissues and cells assessment includes a review and evaluation of relevant processing documentation and an assessment of deviations from specified procedures;
- g) No tissue / cells are released for sale or supply prior to certification by a responsible person.⁸⁷

A.7.2.2. Documentation

1. Laboratory documentation should be consistent with the following principles. An important part of this documentation deals with quality control and the following details should be readily available to the Quality Control Department:

- a) Specifications;
- b) Sampling procedures;
- c) Testing procedures and records (including analytical worksheets and/or laboratory notebooks);
- d) Analytical reports and/or certificates;
- e) Data from environmental monitoring, where required;
- f) Validation records of test methods, where applicable;
- g) Procedures for and records of the calibration of instruments and maintenance of equipment.⁸⁸

2. Any quality control documentation relating to tissues / cells should be retained for at least 30 years after their clinical use.

3. For some kinds of data (e.g. analytical tests results, environmental controls, data included in product/process quality reviews), it is recommended that records are kept in a manner permitting trend evaluation.

4. In addition to the information which is part of the tissues / cells record, other original data such as laboratory notebooks and / or records should be retained and readily available.⁸⁹

A.7.2.3. Sampling

1. The sample taking should be done in accordance with approved written procedures that describe:

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- a) *Method of sampling;*
 - b) *Equipment to be used;*
 - c) *Amount of the sample to be taken;*
 - d) *Instructions for any required sub-division of the sample;*
 - e) *Type and condition of the sample container to be used;*
 - f) *Identification of containers sampled;*
 - g) *Any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;*
 - h) *Storage conditions'*
 - i) *Instructions for the cleaning and storage of sampling equipment.*
2. *Reference samples should be representative of the tissue / cells or materials from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process).*
3. *Sample containers should bear a label indicating the contents, with the tissue / cells code / batch number, the date of sampling and the containers from which samples have been drawn.*
4. *Further guidance on reference and retention samples is given in the following sections.⁹⁰*

A.7.2.4. Testing

1. *Analytical methods should be validated. All testing operations should be carried out according to the approved methods.*
2. *The results obtained should be recorded and checked to make sure that they are consistent with each other. Any calculations should be critically examined.*
3. *The tests performed should be recorded and the records should include at least the following data:*
 - a) *Name of the material or tissue/cells and, where applicable, presentation;*
 - b) *Code/batch number and, where appropriate, the processor and/or supplier;*
 - c) *References to the relevant specifications and testing procedures;*
 - d) *Test results, including observations and calculations, and reference to any certificates of analysis;*
 - e) *Dates of testing;*
 - f) *Initials of the persons who performed the testing;*

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- g) Initials of the persons who verified the testing and the calculations, where appropriate;
 - h) A clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.
4. All the in-process controls, including those made in the processing area by processing personnel, should be performed according to methods approved by Quality Control and the results recorded.⁹¹
 5. Special attention should be given to the quality of laboratory reagents, volumetric glassware and solutions, reference standards and culture media. They should be prepared in accordance with written procedures.
 6. Laboratory reagents intended for prolonged use should be marked with the preparation date and the signature of the person who prepared them. The expiry date of unstable reagents and culture media should be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardisation and the last current factor should be indicated.
 7. Where necessary, the date of receipt of any substance used for testing operations (e.g. reagents and reference standards) should be indicated on the container. Instructions for use and storage should be followed. In certain cases it may be necessary to carry out an identification test and/or other testing of reagent materials upon receipt or before use.⁹²

A.7.2.5. Stability Monitoring

1. After distribution, the stability of the tissues and cells should be monitored according to a continuous appropriate programme that will permit the detection of any stability issue (e.g. integrity, elasticity, changes in levels of impurities or dissolution profile) associated with the presentation in the shipping package.⁹³
2. Due to the variability of the tissues and cells, requirements for stability monitoring should be defined on a case-by-case basis.
3. A documented, on-going testing programme should be designed to monitor the stability characteristics of tissues and cells. The results should be used to confirm appropriate storage conditions and retest dates or expiry dates.

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⁹² EU Good Manufacturing Practices Guidelines

⁹³ EU Good Manufacturing Practices Guidelines

4. *The purpose of the on-going stability programme is to monitor the tissues/cells over its shelf life and to determine that the tissue/cells remains, and can be expected to remain, within specifications under the labelled storage conditions.*⁹⁴

5. Normally three representative tissues / three cells batches should be placed on the stability monitoring programme to confirm the retest or expiry date.

6. Stability testing should be suitable to their shelf-life / retest period and / or batch size. For tissues / cells with a shelf-life of several days a scientific based programme needs to be implemented. For tissues / cells with shelf-lives of at least six months, ICH recommendations should be followed, if the amount of sampled material allows.

7. Where relevant, a stability monitoring programme should be put in place and retain samples in sufficient quantity to permit further examination at a later stage.

8. *The protocol for an on-going stability programme should extend to the end of the shelf life period and should include, but not be limited to, the following parameters:*

- a) *Number of batch(es) per strength and different batch sizes, if applicable;*
- b) *Relevant physical, chemical, microbiological and biological test methods;*
- c) *Acceptance criteria;*
- d) *Reference to test methods;*
- e) *Description of the container closure system(s);*
- f) *Testing intervals (time points);*
- g) *Description of the conditions of storage (standardised ICH conditions for long term);*
- h) *Testing, consistent with the product labelling, should be used);*
- i) *Other applicable parameters specific to the tissues/cells.*

10. *A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.*⁹⁵

A.7.2.6. Expiry Date

1. The expiry or retest date should come from formal stability studies data performed on at least three representative tissues or three cells batches. The tissues and cells should be processed to a minimum of pilot scale and using a method of processing that simulates the final process.

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⁹⁵ EU Good Manufacturing Practices Guidelines

2. A representative sample should be taken for the purpose of performing a retest.

A.7.3. QUALITY RISK MANAGEMENT

1. *Risk management should be integrated into all (primary) processes of TEs, including medical donor screening. Risk management should be used to identify and control risks associated with product quality, reliability and safety. Risk management processes should result in situations where residual risk is within manageable or acceptable limits.*
2. *Risk management principles and methodologies should be incorporated into TE staff training programmes.*
3. *Risk management should serve as documentation of the rationale for key safety or quality related decisions. Risk assessment should be used to support better and more informed decisions on improving organisations and processes.*
4. *Risk management should be used to support decision-making regarding the specific validations that the TE needs to perform. The risk assessment should highlight the critical points in the processes allowing the development of an appropriate validation plan.*
5. *The only circumstances where it can be justified that general requirements are not followed is where a decision is based on risk management by the responsible person. Otherwise all aspects of the EU directives must be followed.*
6. *Risk management should be based on the following steps:*
 - a) *Risk identification;*
 - b) *Risk analysis;*
 - c) *Risk evaluation;*
 - d) *Risk control;*
 - e) *Risk reduction;*
 - f) *Risk acceptance;*
 - g) *Risk review;*
 - h) *Risk communication.⁹⁶*

A.7.4. VALIDATION

A.7.4.1. General

1. TEs should establish documented evidence that provides a high degree of assurance that a specific process, piece of equipment or environment will consistently produce a product meeting its pre-determined specifications and quality attributes.

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2. All critical equipment and technical devices must be identified and validated.⁹⁷
3. All critical processing procedures must be validated and must not render the tissues and cells clinically ineffective or harmful to the recipient⁹⁸.
4. TEs should identify what validation work is needed to prove control of the critical aspects of their particular operations.
5. Significant changes to the facilities, the equipment and the processes, which may affect the quality of the tissues and cells, should be validated.
6. A risk assessment approach should be used to determine the scope and extent of validation. Such risk assessment should take into account all the equipment (e.g. autoclave, incubator, freeze drier), facilities (e.g. clean rooms, laminar flow module), electronic systems (e.g. clean rooms environmental monitoring system, tissues processing system) and processes (e.g. musculoskeletal processing, skin processing, clean rooms disinfection, tissue transport, analytical methods) which may impact on the quality of processed tissues.
7. The results from the risk assessment study regarding the scope of validation activities within a TE should be covered in a Validation Master Plan.

A.7.4.2. Documentation

1. The Validation Master Plan should consist of at least:
 - a) Description of the TE;
 - b) List of equipment, facilities, electronic systems and processes that need to be qualified or validated;
 - c) State of validation of each element within the scope;
 - d) Validation programme;
 - e) Validation activities responsibilities;
 - f) Procedures related to validation activities;
 - g) Criteria for requalification or revalidation;
2. The activities of qualification or validation should be described in a protocol containing at least:
 - a) Objective;
 - b) Scope;
 - c) Responsibilities;

⁹⁷ Commission Directive 2006/86/EC (Annex I)

⁹⁸ Commission Directive 2006/86/EC (Annex II)

- d) Related documents;
- e) Stages of qualification or validation;
- f) Acceptance criteria.

3. A validation / qualification report should be issued reflecting the results of the activities containing at least:

- a) Objective;
- b) Scope;
- c) Responsibilities;
- d) Related documents;
- e) Deviations from the protocol;
- f) Results;
- g) Conclusions.

A.7.4.3. Facility, system and equipment qualification

A.7.4.3.1. Qualification for new facilities, systems and equipment

1. The first element of the validation of new facilities, systems or equipment could be Design qualification (DQ: documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose). During DQ the compliance of the design with GTP should be demonstrated and documented.

2. Installation qualification (IQ: documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements) should be performed on all critical facilities, systems and equipment. The IQ protocol should include, but not be limited to:

- a) Verification that all items of equipment / facility fall under the requirements of the purchase order;
- b) Verification of CE-approval (if required for the equipment);
- c) Verification that the location and environmental conditions of the equipment / installation are correct according to the manufacturer's recommendations and internal specifications;
- d) Verification that items are installed in accordance with internal specifications and identified correctly by manufacturer;
- e) Verification of serial numbers of all items/parts;
- f) Verification that all parts of the equipment are free from defects;
- g) Verification that the connection of electricity, water, steam, pressure, vacuum, etc. are functional and that their operating ranges are appropriate for the proper functioning of the installation;

- h) Identification of the action of the items that require calibration. Check for appropriate calibration certificates and programme and procedure for periodic calibration;
- i) Checking for instructions for use and cleaning of equipment / manufacturer manual and log book of operations of the unit / installation;
- j) Verification of the existence of instructions for performing preventive maintenance.

3. *Operational qualification* (OQ: documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges) should follow IQ. The OQ protocol should include, but not be limited to the following:

- a) Tests that have been developed from knowledge of processes, systems and equipment;
- b) Tests to include a condition or a set of conditions encompassing upper and lower operating limits, sometimes referred to as ‘worst case’ conditions;
- c) Identification of critical operating variables, tests performed, alarms, security devices and acceptance criteria;
- d) Verification that the operation of various items of equipment / installation connected to the mains and put into operation is correct.

4. *The completion of a successful OQ should allow the finalisation of calibration, operating and cleaning procedures, operator training and preventative maintenance requirements. It should permit a formal ‘release’ of the facilities, systems and equipment.⁹⁹*

5. *Performance qualification* (PQ: documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications) should follow successful completion of IQ and OQ. Although PQ is described as a separate activity, it may in some cases be appropriate to perform it in conjunction with OQ, or concurrently with production activities. The PQ protocol should include, but not be limited to, the following:

- a) Tests, using production materials, qualified substitutes or simulated product, that have been developed from knowledge of the process and the facilities, systems or equipment;
- b) Tests to include a condition or set of conditions encompassing upper and lower operating limits;
- c) Process description or reference to protocol development and / or conditioning to validate;
- d) List of equipment involved;
- e) Critical parameters and operating ranges;

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- f) Reference of the procedures involved;
- g) Description of the tests to be performed, or control variables, sample taking, time and reference method sampling and analytical methods;
- h) Acceptance criteria.

A.7.4.3.2. Qualification of established (in-use) facilities, systems and equipment

1. Evidence should be available to support and verify the operating parameters and limits for the critical variables of the operating equipment.
2. The calibration, cleaning, preventative maintenance, operating procedures and operator training procedures and records of the in-use facilities / systems / equipment should be documented.¹⁰⁰

A.7.4.3.3. Qualification of Clean Rooms

Following the steps described in the Facilities, Systems and Equipment Qualification section A.2., the tests to be carried out for the Clean Rooms should include at least:

- a) Air change (renewal) rate per hour within one room: the speed and rate of renewals per hour according to specified will be checked;
- b) Smoke test for air flow within each room;
- c) Absolute filters integrity: the grade of sealing of the filters and the absence of leaks in the filter material will be checked;
- d) Particle counting: the total count of airborne particles (viable or not) will be checked according to specifications;
- e) Temperature / relative humidity: the temperature and relative humidity will be recorded during the test and will be checked according to specifications;
- f) Differential pressure: the pressure differential between the different areas will be checked according to specifications;
- g) Recovery test (normally tested for A and B classified clean rooms): the time required for a clean room to recover the specified classification after an out-of-specifications will be checked;
- h) Laminar flow velocities in laminar flow areas;
- i) HVAC system operations and alarms;
- j) Electricity back-up systems.

All these tests should be performed at least in an ‘at rest’ situation. Additionally, the particle counting test should be performed also in an ‘in operation’ situation.

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A.7.4.3.4. Qualification of Laminar Flow Hoods

Following the steps described in the Facilities, Systems and Equipment Qualification paragraph A.2, the tests to be carried out for the laminar flow hoods will include at least:

- a) Speed and uniformity of the air: the average speed meets the specified acceptance criteria and that there is uniformity will be checked;
- b) Absolute filters integrity: the grade of sealing of the filters and the absence of leaks in the filter material will be checked;
- c) Particle counting: the total count of airborne particles (viable or not) will be checked according to specifications;
- d) Electronic test: all the operating controls will be checked (light, UV light, fan) and alarms;
- e) Smoke Test (for biological safety cabinets). The test objective is to study the behaviour of air inside and outside the cabin with the help of a smoke generator.

All these tests should be performed at least in an ‘at rest’ situation. Additionally, the particle counting test should be performed also in an ‘in operation’ situation.

A.7.4.4. Process validation

- 1. Facilities, systems and equipment to be used should have been qualified and analytical testing methods should be validated.
- 2. Processes in use for some time should also be validated.
- 3. Staff taking part in the validation work should have been appropriately trained.
- 4. Facilities, systems, equipment and processes should be periodically evaluated to verify that they are still operating in a valid manner.

A.7.4.4.1. Prospective validation

- 1. Process validation should normally be completed prior to the distribution of any tissue or cell (prospective validation).
- 2. *Prospective validation should include, but not be limited to the following:*
 - a) *Short description of the process;*
 - b) *Summary of the critical processing steps to be investigated;*
 - c) *List of the equipment/facilities to be used (including measuring / monitoring / recording equipment) together with its calibration status;*
 - d) *Finished product specifications for release;*
 - e) *List of analytical methods, as appropriate;*
 - f) *Proposed in-process controls with acceptance criteria;*

- g) Additional testing to be carried out, with acceptance criteria and analytical validation, as appropriate;
 - h) Sampling plan;
 - i) Methods for recording and evaluating results;
 - j) Functions and responsibilities;
 - k) Proposed timetable.
3. Using this defined process (including specified components) a series of batches of the final tissues or cells may be produced under routine conditions.
4. The number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters would constitute a validation of the process.
5. Batches, where applicable, made for process validation should be the same size as the routine scale batches.¹⁰¹

A.7.4.4.2. Concurrent validation

1. In exceptional circumstances it may be acceptable not to complete a validation program before routine production starts and to validate processes during routine production (concurrent validation). The decision to carry out concurrent validation must be justified, documented and approved by authorised personnel.
2. Documentation requirements for concurrent validation are the same as specified for prospective validation.¹⁰²

A.7.4.4.3. Retrospective validation

1. Retrospective validation is only acceptable for well-established processes.
2. Retrospective validation will be inappropriate where there have been recent changes in the composition of the tissues or cells, operating procedures or equipment. Validation of such processes should be based on historical data. The steps involved require the preparation of a specific protocol and the reporting of the results of the data review, leading to a conclusion and a recommendation.
3. The source of data for this validation should include, but not be limited to:

¹⁰¹ EU Good Manufacturing Practices Guidelines

¹⁰² EU Good Manufacturing Practices Guidelines

- a) Batch processing and packaging records;
 - b) Process control charts;
 - c) Maintenance log books;
 - d) Records of personnel changes;
 - e) Process capability studies;
 - f) Finished product data;
 - g) Including trend cards;
 - h) Storage stability results.
4. Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency.
5. Additional testing of retained samples may be needed to obtain the necessary amount or type of data to retrospectively validate the process.
6. For retrospective validation, generally data from ten to thirty consecutive batches should be examined to assess process consistency, but fewer batches may be examined if justified.¹⁰³

A.7.4.5. Cleaning and Disinfection Validation

1. Cleaning and disinfection validation should be performed in order to confirm the effectiveness of a cleaning or disinfection procedure.
2. The rationale for selecting limits of carry over of product residues, cleaning agents and microbial contamination should be logically based on the materials involved. The limits should be achievable and verifiable.
3. Residues of products or cleansing agents should be checked based on risk assessment. Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant.
4. Normally only cleaning or disinfection procedures for product contact surfaces of the equipment need to be validated. Consideration should be given to noncontact parts.
5. The intervals between use and cleaning or disinfection as well as cleaning or disinfection and reuse should be validated.
6. Cleaning or disinfection intervals and methods should be determined.

¹⁰³ EU Good Manufacturing Practices Guidelines

7. For cleaning and disinfection procedures for products and processes which are similar, it is considered acceptable to select a representative range of similar products and processes. A single validation study utilising a “worst case” approach can be carried out which takes account of the critical issues.
8. Typically three consecutive applications of the cleaning or disinfection procedure should be performed and shown to be successful in order to prove that the method is validated.
9. ‘Test until clean’, is not considered an appropriate alternative to cleaning validation.
10. Products which simulate the physicochemical properties of the substances to be removed may exceptionally be used instead of the substances themselves, where such substances are either toxic or hazardous.¹⁰⁴

A.7.4.6. Revalidation

1. Revalidation should be performed when there is a change in any equipment, facilities or process, considered significant because it affects the quality of the product / process or have implications for the current European regulations. These changes should be approved through a change control procedure.
2. When the product quality review confirms that the system or process is consistently producing material meeting its specifications, there is no need for revalidation.

A.7.5. CRITICAL THIRD PARTY AGREEMENTS

1. TEs shall establish written agreements with a third party each time an external activity takes place which influences the quality and safety of tissues and cells processed in co-operation with a third party, and in particular in the following circumstances:
 - a) Where a TE entrusts one of the stages of tissue or cell processing, control, packaging, storing or distribution to a third party;
 - b) Where a third party provides goods and services that affect tissue or cell quality and safety assurance, including their distribution;
 - c) Where a TE provides services to a TE which is not accredited;
 - d) Where a TE distributes tissue or cells processed by third parties.¹⁰⁵,
2. The written agreements should include at least:
 - a) A clear description of the scope of the agreement;

¹⁰⁴ EU Good Manufacturing Practices Guidelines

¹⁰⁵ Directive 2004/23/EC of the European Parliament and of the Council (Art 24)

- b) Names, roles and signatures of those taking responsibility for each party;
- c) Detailed description of the responsibilities of each party in relation to safety and quality of tissues, including any quality system requirements considered necessary;
- d) Provision for auditing of the third party by tissue establishment staff on a routine and/or exceptional basis;
- e) Requirements for data protection where third parties have access to any information of a personal nature (donor or recipient);
- f) Requirements for maintenance of traceability for tissues and any materials that come into contact with them;
- g) Requirements for archiving of traceability and quality system records;
- h) Any requirements for certification/licensing of the third party that might be appropriate (e.g. in the case of a serology testing laboratory);
- i) Duration of the agreement and the timing of reviews;
- j) Details of when and how adverse incidents (reactions or events) should be communicated between the TE and the third party and how they should be investigated;
- k) The way in which the Responsible Person releasing the tissue/cell batch for application ensures that any critical step performed by a third party was carried out in compliance with the requirements laid down;
- l) Where tissue processing is carried out by a third party, the agreement should specify who is responsible for purchasing materials, testing and releasing materials, undertaking processing and quality controls, including in-process controls, and who has responsibility for sampling and analysis;
- m) Where relevant, processing, analytical and distribution records, and reference samples should be kept by, or be available to, the tissue establishment. Any records relevant to assessing the quality of tissue/cells in the event of complaints or a suspected defect must be accessible and specified in the defect/recall procedures of the Contract Giver;
- n) The contract should permit the competent authorities to inspect the third party if they wish to do so;
- o) The way in which data and samples affecting the traceability, quality or safety of tissues and cells, are provided to the tissue establishment in case of resolution of the agreement.

3. TEs shall evaluate and select third parties on the basis of their ability to meet the standards laid down in 2004/23/EC.

4. TEs shall keep a complete list of the agreements that they have established with third parties.

5. Agreements between TEs and third parties shall specify the responsibilities of the third parties and detailed procedures.

6. TEs shall provide copies of agreements with third parties at the request of the competent authority or authorities.¹⁰⁶

A.7.6. CONTINUITY PLANS / CESSATION OF BANK

1. Member States shall ensure that TEs have agreements and procedures in place to ensure that, in the event of termination of activities for whatever reason, stored tissues and cells shall be transferred to other tissue establishment or establishments accredited, designated, authorised or licensed in accordance with Article 6 (Directive 2004/23/EC), without prejudice to Member States' legislation concerning the disposal of donated tissues or cells, according to the consent pertaining to them.¹⁰⁷
2. TEs should have in place a continuity plan (with adopted procedures and concluded agreements) to ensure that, in the event of termination of their banking/servicing activities (partly, temporarily or permanently) for whatever reason, the tissues in their management should be transferred to other TEs.
3. This continuity plan should not undermine legitimate public health interests and should not be guided by financial considerations (profit-maximizing practices).
4. When the continuity plan implies that tissue could be exported (transferred to a country outside the EU), the export should comply with the requirements in section A.6.3. (Import and export).
5. The accepting TEs need to be accredited, designated, authorized or licensed for the purpose of the activities they will need to assume when accepting the tissue.
6. The accepting TEs need to be able to handle the anticipated amounts of transferred tissue (e.g. sufficient stocking capacity).
7. The transferred tissue needs to be accompanied by its relevant documentation (including traceability data) and material concerning the quality and safety of the tissue (including retention samples).
8. The transport conditions should maintain the quality and safety of the tissues.
9. The transfer of tissues, documentation and material are done under the responsibility of the Responsible Persons of the giver and acceptor TEs.

¹⁰⁶ Directive 2004/23/EC of the European Parliament and of the Council (Art 24)

¹⁰⁷ Directive 2004/23/EC of the European Parliament and of the Council (Art 21)

10 The acceptor TEs should have in place procedures for verifying the compliance of the tissues to the ethical and legal requirements.

11. The terms and conditions of the transfer of tissues should be described in an agreement (service level agreement or convention) detailing at least:

- a) Responsibilities and commitments of each party;
- b) Type and anticipated quantities of tissues that will be transferred;
- c) Type and anticipated quantities of documentation that will be transferred;
- d) Type and anticipated quantities of material (e.g. retention samples) that will be transferred;
- e) Transport conditions for tissue, documentation and material.

It is possible, however, that a meaningful transfer of tissues cannot be agreed upon (or is impossible). In this case, the CA should determine the fate of the tissues.

A.8. BIOVIGILANCE

A.8.1. SERIOUS ADVERSE EVENTS/REACTIONS

1. Any adverse event occurring during procurement that has or may have resulted in harm to a living donor and the outcome of any investigation to determine the cause must be recorded and reviewed.¹⁰⁸

2. Member States shall ensure that there is a system in place to report, investigate, register and transmit information about serious adverse events and reactions which may influence the quality and safety of tissues and cells and which may be attributed to the procurement, testing, processing, storage and distribution of tissues and cells, as well as any serious adverse reaction observed during or after clinical application which may be linked to the quality and safety of tissues and cells.

3. All persons or establishments using human tissues and cells regulated by this Directive shall report any relevant information to establishments engaged in the donation, procurement, testing, processing, storage and distribution of human tissues and cells in order to facilitate traceability and ensure quality and safety control.

4. The responsible shall ensure that the competent authority or authorities is or are notified of any serious adverse events and reactions and is or are provided with a report analysing the cause and the ensuing outcome.

¹⁰⁸ Commission Directive 2006/17/EC (Annex IV)

5. *The procedure for notifying serious adverse events and reactions shall be established by the Commission.*

6. *Each TE shall ensure that an accurate, rapid and verifiable procedure is in place which will enable it to recall from distribution any product which may be related to an adverse event or reaction.¹⁰⁹*

7. In cases of disease transmission or infection through the implanted tissues and cells, necessary measures should be taken, including:

- a) Immediate notification of severe reactions to the competent authority;
 - i. Inherent measures according to traceability requirements (information related to implantation centres and recovery centres);
 - ii. Recall of the tissues and cells which have already been distributed but not used;
 - iii. Stopping the distribution of all tissues and cells involved and recall those remaining in stock (both in the TE or in a third party facilities).
- b) Immediate measures for tissue isolation;
 - i. Evaluation of predictable actions during the process and implementation of corrective measures and / or preventing actions when appropriate;
 - ii. Report of the measures taken provided to the competent authority.

A.8.2. NOTIFICATION OF SERIOUS ADVERSE REACTIONS (RECIPIENTS)

1. All adverse events and reactions that are suspected of being related to the quality and safety of tissues or cells should be notified to TEs to allow trends in minor events and reactions to be monitored for continuous improvement purposes.

2. TEs should then apply the adequate tools to assess the severity, the imputability and the impact, in collaboration with appropriate stakeholders, and to identify those serious adverse events and reactions that should be notified to competent authorities.

3. Clinical symptoms or situations suggesting that any of the following reactions might have occurred in a tissue or cell recipient (abbreviated descriptions in brackets) should be seen as triggers for an adverse reaction report. Note that the list is not exhaustive.

- a) Unexpected primary infections possibly transferred from the donor to recipient (e.g. viral, bacterial, parasitic, fungal, prion) (**Infection - Donor**);
- b) Transmitted infection (viral, bacterial, parasitic, fungal, prion) possibly due to contamination or cross-contamination by an infectious agent on the procured tissues,

¹⁰⁹ Directive 2004/23/EC of the European Parliament and of the Council (Art 11)

- cells or associated materials from procurement to clinical application (**Infection – Tissue/cells**);
- c) Hypersensitivity reactions, including allergy, anaphylactoid reactions or anaphylaxis (**Hypersensitivity**);
 - d) Malignant disease possibly transferred by the tissue / cells (whatever the origin, donor or process) (**Malignancy**);
 - e) Unexpectedly delayed or absent engraftment, graft failure (including mechanical failure) (**Failure**);
 - f) Toxic effects from tissues and cells or associated materials (**Toxicity**);
 - g) Unexpected immunological reactions due to tissue / cell mismatch (**Mismatch**);
 - h) Aborted procedure involving unnecessary exposure to risk e.g. wrong tissue supplied, discovered after patient is anaesthetised and the surgical procedure has begun (**Undue Risk**);
 - i) Suspected transmission of genetic disease (**Genetic Abnormality**);
 - j) Suspected transmission of other (non-infectious) illness (**Other Transmission**).

A.8.3. NOTIFICATION OF SERIOUS ADVERSE REACTIONS (LIVING DONORS)

1. Donor adverse reactions with a possible direct effect on the quality and safety of tissue/cells must be reported. These may be immediate (i.e. occurring at the time of the donation or within eight days of donation) or they may be delayed [i.e. identified after the donation (possibly even many years later)].
2. Where allogeneic living donors have been harmed by a donation process but there is no detrimental impact on the quality or safety of the specific tissues or cells concerned, a serious threat to the supply of those tissues or cells could result from the loss of public willingness to donate, or there may be implications for the safety of other living donors. On this basis, it is recommended that competent authorities include reporting of such donor adverse reactions in their tissue and cell vigilance programmes and in their annual reports to the EC. If such reactions are the result of an administered drug, it will be reportable through the pharmacovigilance system. It should not be reported again through the tissue and cell vigilance system but appropriate communication links between responsible authorities should ensure that the tissue and cell competent authority is aware of these reactions.

A.8.4. NOTIFICATION OF SERIOUS ADVERSE EVENTS

1. An adverse event can be detected at any stage in the process from donation to transplantation. Competent authorities will not want to be informed about every deviation from an SOP within a TE. Only serious adverse events should be reported to the CA.

2. Seriousness might relate to potential severity of an adverse reaction if the event had not been discovered or to the severity of an adverse reaction that might occur due to a repetition of the event in another place or time.
3. Deviations from standard operating procedures in TEs, or other adverse events, which have implications for the quality and safety of tissues and cells should result in SAE reporting to the competent authority when one or more of the following criteria applies:
 - a) Inappropriate tissues / cells have been distributed for clinical use, even if not used;
 - b) The event could have implications for other patients or donors because of shared practices, services, supplies or donors;
 - c) The event resulted in loss of any irreplaceable autologous tissues or cells or any highly matched (i.e. recipient specific) allogeneic tissues or cells;
 - d) The event resulted in the loss of a significant quantity of unmatched allogeneic tissues or cells.
4. Thus, where the criteria listed above are met, the adverse event can be considered as posing a serious risk to patient health and in those circumstances it should be reported to the CA. Events that are commonly referred to as ‘near misses’ are included in the above mentioned categories. In the case of assisted reproduction, any type of gamete or embryo misidentification or mix-up is considered to be a serious adverse event and should be notified to the CA.

SECTION B: SPECIFIC OCULAR REQUIREMENTS

B.1 DONOR SCREENING

B.1.1. ACTIVITIES

B.1.1.1.Donor detection

See generic requirements in section A.3.1.1

B.1.1.2.Donor consent

See generic requirements in section A.3.1.2

B.1.1.3. Donor evaluation

B.1.1.3.1.General

The suitability of a specific individual for eye tissue and placental tissue donation should be documented and should be based on medical and social history, clinical status, physical assessment, testing and autopsy (if performed) according to the generic EU GTPs (see generic requirements in section A.1.).

B.1.1.3.2. Medical evaluation

See generic requirements in section A.3.1.6.

B.1.1.3.2.1.Anamnesis

See generic requirements in section A.3.1.6

B.1.1.3.2.2.Social evaluation

See generic requirements in section A.3.1.6.3

B.1.1.3.2.3. Physical evaluation

1. All prospective ocular tissue donors should undergo a thorough physical examination as close as possible prior to donation with special attention to physical signs of HIV disease, infectious hepatitis, and injecting illegal drug use (see generic requirements in section A.3.1.6.4). Additionally gross inspection of the orbit with special concentration on the cornea with a view to the medical contra indications (see A.3.1.6.5) should be performed. Each eye bank should have a consistent policy for conducting and documenting this examination.

B.1.1.3.2.4.Exclusion criteria

1. The selection criteria for ocular tissue donors are based on a risk analysis in relation to the use of the donor tissue. Indications for such risks are to be identified with the help of anamnesis, appropriate sources such as donor's medical files and consultation of treating physicians, biological testing, post mortem examination, and other suitable examinations, e.g. autopsy results. Unless the donation is justifiable based on a documented risk evaluation performed by the responsible person, donors are to be excluded from donating, if one or more of the exclusion criteria should apply.
2. The *Minimum* set of contraindications for use of ocular tissue for transplant purposes are set out below. Individual eye banks may have additional exclusionary criteria. Some criteria listed as generally exclusionary may be acceptable depending on the storage method used for tissue preservation.

B.1.1.3.2.4.1.Exclusion criteria for cornea donors: Penetrating Keratoplasty

1. In addition to the exclusion criteria mentioned section A.3.1.6.5. of the generic GTP requirements, screening of ocular tissue donors should be conducted for the following disorders, which are potentially health threatening for the recipient(s) or pose a risk to the success of the surgery, and should not be offered for surgical purposes:

B.1.1.3.2.4.1.1.Post Mortem Time

Corneal preservation should occur as soon as possible after death, however no later than seventy two (72) hours post mortem for donor corneas intended for organ culture, and no later than sixteen (16) hours post mortem for donor corneas intended for short-time cultivation (hypothermic storage). All time intervals for each donor (death to enucleation and preservation) should be recorded.

B.1.1.3.2.4.1.2. Eye diseases and ocular surgery

- a) Ocular inflammation (including known ocular involvement by systemic disease);
- b) Congenital or acquired disorders of the eye or previous ocular surgery that would prejudice graft outcome;.
- c) Malignant tumours of the anterior segment;.
- d) Receipt of a corneal, scleral or limbal graft;
- e) Malignant tumours of the eye e.g. retinoblastoma, melanoma, adenocarcinoma; also congenital, malignant posterior chamber-tumours;

- f) Corneal disorders including keratoconus, keratoglobus, dystrophy;
- g) Corneal opacity, scarring, or pterygium, which involves the central optical area of the corneal button (may be considered for posterior lamellar procedures).

Intrinsic eye disease

- a) Active ocular or intraocular inflammation: conjunctivitis, keratitis, scleritis, iritis, uveitis, vitritis, choroiditis, retinitis;
- b) Congenital or acquired disorders of the eye that would preclude a successful outcome for the intended use, e.g., a central donor corneal scar for an intended penetrating keratoplasty, keratoconus, and keratoglobus;
- c) Pterygia or other superficial disorders of the conjunctiva or corneal surface involving the central optical area of the corneal button.

Prior intraocular or anterior segment surgery

- a) Refractive corneal procedures, e.g., radial keratotomy, lamellar inserts, etc.
- b) Laser photoablation surgery is allowed to be used in cases of tectonic grafting and posterior lamellar procedures.
- c) Corneas from patients with anterior segment (e.g., cataract, intraocular lens, glaucoma filtration surgery) may be used if screened by specular microscopy and meet the Eye Bank's endothelial standards.
- d) Laser surgical procedures such as argon laser trabeculoplasty, retinal and panretinal photocoagulation do not necessarily preclude use for penetrating keratoplasty but should be cleared by the medical director.
- e) Corneal surgery e.g. radial keratotomy, laser refractive surgery: photorefractive keratectomy (PRK) or laser in situ keratomileusis (LASIK)
- f) Excimer (Lasik, Lasek etc.), past PKPs and other refractive surgeries (ast. KT, PTK, rad. KT etc.) are not acceptable if usage is planned for PKP, DALK, LKP; if usage is planned for DLEEK, DSAEK it would be acceptable.

Many defects or disorders, and many surgeries on the eye e.g. for cataract removal, glaucoma, retinal therapy are not contraindications, where corneal tissue is screened by endothelial microscopy. They should not be considered contraindications to donation but the cornea should be assessed for suitability for the intended surgical procedure.

B.1.1.3.2.4.1.3. Infections

Persons with significant local bacterial, viral, parasitic or mycotic infection including meningitis of the eye cannot be considered as ocular tissue donors.

Donors suffering from bacterial forms of septicaemia may be acceptable at the discretion of the eye bank medical director but only when the corneas are stored in an organ culture which allows detection of a potential bacterial contamination of the tissue.

B.1.1.3.2.4.1.4. Invalid laboratory test results

Tissue banks may only accept tissue from donors with a plasma dilution of more than fifty (50) per cent, if the test methods applied to such plasma are validated.

B.1.1.3.2.4.1.5. Vaccination

Persons who received a post-expositional vaccination against rabies within the last twelve (12) months or a live vaccination, e.g. against poliomyelitis, yellow fever, rubella, measles, mumps, within the last four (4) weeks prior to removal of the cornea cannot be considered as donors.

B.1.1.3.2.4.1.6. Malignancies

Donors suffering from malignant diseases may be considered for cornea donation, except donors suffering from retinoblastoma, haematological neoplasia and malignant tumours of the fundus.

B.1.1.3.2.4.1.7. Donor age

Provided that corneas are examined to exclude those with inadequate endothelium, no upper donor age limit needs to be set, but other age-related corneal changes must be taken into account. The lower age limit is less certain and will depend on surgical demand.

B.1.1.3.2.4.2. Exclusion criteria for ocular tissue donors: Anterior Lamellar or Patch Keratoplasty

Criteria are the same as listed for penetrating keratoplasty except that tissue with local eye disease affecting the corneal endothelium or previous ocular surgery that does not compromise the corneal stroma e.g. aphakia, iritis, is acceptable for use. Death to preservation time may be extended.

B.1.1.3.2.4.3. Exclusion criteria for ocular tissue donors: Posterior Lamellar / Endothelial Keratoplasty

Criteria are the same as listed for penetrating keratoplasty except that tissue with local non-infectious anterior pathology that does not affect the posterior stroma and endothelium is

acceptable for use. Surgeons should be notified of any such pathology prior to placing the tissue for transplant.

B.1.1.3.2.4.4. Exclusion criteria for ocular tissue donors: Epikeratoplasty

Criteria are the same as listed for penetrating keratoplasty except that tissue with local eye disease affecting the corneal endothelium e.g. aphakia, iritis, is acceptable for use. Death to preservation time may be extended.

B.1.1.3.2.5. Exclusion criteria for scleral tissue donors

Criteria are the same as listed for penetrating keratoplasty except that tissue with local eye disease affecting the cornea is acceptable for use. Death to preservation time may be extended.

B.2. RECOVERY

B.2.1. ACTIVITIES

B.2.1.1. Access to the operating room or other recovery room

See generic requirements in section A.4.1.1.

B.2.1.2. Recovery

B.2.1.2.1. General

See generic requirements in section A.4.1.3.1.

B.2.1.2.2. Deceased donors

Except for the room, the entire retrieval of the donor cornea and sclera is to be performed analogous to ophthalmic surgery in a living patient. Retrieval may be either by removal of the whole eye (enucleation) or by removal of only the corneoscleral button (in situ excision). Tissue recovery is to be performed using validated aseptic procedures.

B.2.1.2.2.1. Donor identification

Prior to tissue recovery, the donor should be positively identified by cross-check with a tag or other label on the body, or by positive identification by hospital or mortuary staff.

B.2.1.2.2.2. Gowning

Staff performing the retrieval is to be dressed appropriately for the kind of retrieval to minimize the risk of contamination of the tissue to be removed and also the hazard for the

performing staff. This includes due disinfection (surgical hand disinfection), sterile clothes as well as wearing sterile gloves, face mask or protective mask and surgery cap.

B.2.1.2.2.3. Donor preparation

The donor eyes should be flushed with a balanced sterile saline solution to remove all debris, mucus and foreign matter from the cornea and conjunctival sack. Irrigation will also reduce microbial contamination. A broad-spectrum antibiotic / antifungal ophthalmic solution may be used for further moistening the eyes. Subsequent to an effective disinfection of donor skin in the eye area and conjunctiva using a suitable disinfectant (e.g. PVD iodine), a local sterile area is to be created in the area of retrieval using sterile cloths. Hereafter, either the whole eye or the corneoscleral disc is to be recovered. The recovery methods are described in Section A.4.

B.2.1.2.2.4. Whole eye retrieval by enucleation

Enucleation should be performed analogous to ophthalmic surgery in a living patient. After enucleation, the bulbus should be placed in a fixed position (avoiding contact with the cornea and the container) in a moist chamber with sterile physiological electrolytic solution (see 2.3.5). Broad-spectrum ophthalmic antibiotic drops may be used to further minimize bacterial contamination. Containers with the eye should be secured tight and labelled.

The appearance of the donor is to be restored using appropriate prostheses or other material suitable for this purpose. Also any visible disinfection solution is to be wiped off from the donor's skin. And when needed, the donor lids should be closed by tissue glue.

B.2.1.2.2.5. Corneoscleral disc retrieval by in situ excision

Corneoscleral disc in situ excision should be performed analogous to ophthalmic surgery in a living patient. Peritomy should be performed to incise the conjunctiva in a circle as close to the limbus as possible. Sclerotomy should be performed by making an incision through the sclera 2-3mm from the limbus. Care should be taken not to penetrate the underlying choroid. Any trauma and stress to the cornea during incision and scissoring, as well as during the subsequent ciliary body detachment should be avoided.

After in situ excision the corneoscleral disc should be immersed in an appropriate corneal storage solution. And when needed, the donor lids should be closed by tissue glue.

B.2.1.2.2.6. Scleral tissue recovery

Scleral tissue should be recovered from a whole eye on whole eye retrieval by enucleation).

B.2.1.3. Processing during recovery

See generic requirements in section A.4.1.4.

B.2.1.4. Quality control

See generic requirements in section A.5.1.4.

B.2.1.5. Packaging and labelling

See generic requirements in section A.4.1.5.

B.2.1.5.1. Primary packaging and labelling

Subsequent to retrieval, the obtained donor corneas or eyes are to be packaged in a way to minimize the contamination risk. Each tissue is to be packed separately in separate containers and labelled immediately after recovery.

B.2.1.5.1.1. Packaging for organ culture

The organ culture system provides a functional assessment of the cornea during the prolonged storage time (compared to the hypothermic storage).

For subsequent packaging of corneoscleral complex, tissue banks should use a sterile, air tight sealable container containing appropriate normothermic corneal storage medium in accordance with manufacturer's recommendations. The culture medium is an essential factor to guarantee the quality and safety of the donor cornea. For this reason, an established medium for the purpose of corneal preservation is to be used (e.g. MEM). The addition of foetal calf serum is only permissible under the following preconditions:

- a) Serum from 'BSE free' livestock (manufacturer's certificate);
- b) Negative test result for mycoplasma;
- c) Sterile filtered serum.

B.2.1.5.1.2. Packaging for hypothermic storage

For packaging for hypothermic storage of a corneoscleral disc, tissue banks should use an air tight sealable container containing hypothermic corneal storage medium (e.g. OptisolGS) in accordance with manufacturer's recommendations. The medium is to maintain the endothelial cell morphology and thinness of the cornea.

B.2.1.5.1.3. Whole eye packaging / Moist Chamber Storage

An enucleated eye is to be placed in a sterile, air tight sealable chamber together with gauze, moistened by physiological electrolytic solution or antibiotic solution, and then placed at 4°C.

The eye must not be immersed in solution as it will be absorbed by the cornea and cause stromal oedema.

B.2.1.5.1.4. Scleral tissue packaging

Scleral tissue is part of the whole eye and, after whole eye recovery, should be packaged accordingly (see B.2.1.5.1.3. Whole eye packaging / Moist chamber storage).

B.2.1.5.2. Packaging for cryopreservation

Eye banks should use an appropriate package and cryopreservation medium in accordance with regulatory requirements.

B.2.1.6. Storage and transport after recovery

See generic requirements in section A.4.1.6.

B.2.1.6.1. Storage after tissue recovery

B.2.1.6.1.1. Storage temperatures

The donor eyes / corneas are to be stored at temperatures appropriate to maintain their characteristics and biological functions suitable for the intended operation. These temperatures principally correspond to the storage temperatures specified below independent of the method of cultivation.

- a) The donor corneas obtained for organ cultivation by corneoscleral complex excision should be stored in organ culture medium at temperatures from +10 to +40°C.
- b) The donor eyes and corneoscleral discs for hypothermic storage / moist chamber storage should be stored cold at temperatures between +1° and +10°C (e.g. using cooling elements). Temperatures below 0°C are to be strictly avoided.
- c) Corneas for cryopreservation for long-term storage (intended for the purposes of tectonic (structural) keratoplasty only) should be stored by freezing at sub-zero temperatures between -75°C to -196°C. It must be recognized that the functional integrity of the corneal endothelium will be lost, and eye banks may elect to remove the endothelium before storage by this method.

B.2.1.6.1.2. Storage time

Corneas typically must be transplanted as a viable living tissue. The aim of any current corneal storage technique (except cryopreservation) is simply to maintain this living viable state while holding the cornea for the period between donation and transplantation. Maximum storage time of ocular tissues in organ culture or hypothermic solution depends on the storage medium used. The storage time should not exceed the maximum storage time prescribed by the medium / solution manufacturer, or the maximum storage time determined

by the tissue bank validation process. Recommended maximum storage times are presented below.

A minimum storage period is mandatory to allow for proper microbiological testing of the tissue, or the solution in which the tissue is stored. The efficacy of this quarantine period should be evaluated and validated.

B.2.1.6.1.2.1. Organ culture

The maximum recommended storage time by organ culture is 30 days (depending on the medium used) but the storage time may be extended upon the approval of the Medical Director and agreement with the transplanting surgeon.

B.2.1.6.1.2.2. Hypothermic storage

The maximum recommended storage time in hypothermic storage where a viable endothelium is required is 14 days (depending on the medium used) but this may be extended upon the approval of the Medical Director and agreement with the transplanting surgeon. A longer period is acceptable if the endothelium does not need to be viable which should be decided by the Medical Director.

B.2.1.6.1.2.3. Whole eye

The maximum recommended storage time of whole eye in moist chamber storage is 48 hours. However, the time may be extended upon the approval of the Medical Director and agreement with the transplanting surgeon.

B.2.1.6.1.2.4. Corneal cryopreservation

The maximum recommended storage time by corneal cryopreservation is two years. However, this may be extended upon the approval of the Medical Director and agreement with the transplanting surgeon.

B.2.1.6.1.2.5. Scleral tissue

After recovery the scleral tissue is part of the whole eye and should be stored accordingly.

B.2.1.6.2. Transport after tissue recovery

The donor eyes / corneas are to be transported at appropriate temperatures to maintain their characteristics and biological functions. Principally these temperatures correspond to the storage temperatures (see chapter B.2.1.6.1.1), depending on the tissue and the method of cultivation.

The package and the mode of transport are to be chosen in a way as to ensure maintenance of the tissue specific storage temperatures (see chapter B.2.1.6.1.1). This is to be monitored by the tissue bank at regular intervals. If temperature stability should not be reliably guaranteed by the pack or mode of transport used, also in cases of unexpectedly high or low environmental temperatures, a temperature recording unit is to be enclosed that is to measure the temperature inside the pack in minimally half-hour intervals and the data saved. In addition, the pack is to prevent contamination by persons in charge of tissue packaging and transport.

The transport time of donor placentas should be kept as short as possible.

B.2.1.7. Documentation and release for processing

See generic requirements in section A.4.1.7.

B.3. PROCESSING

B.3.1. ACTIVITIES

B.3.1.1. Reception

See generic requirements in section A.5.1.5.

B.3.1.2. Access to the processing facilities

See generic requirements in section A.5.1.2.

B.3.1.3. Processing

B.3.1.3.1. General

See generic requirements in section A.5.1.3

B.3.1.3.2. Processing methods

Proof is required that the validated procedures are performed by the tissue bank staff in a uniform manner in accordance with the approved standard operating procedures (e.g. standardization of corneal endothelial cell counting among the processing staff is required.)

B.3.1.3.2.1. Processing of tissues and cells

See generic requirements in section A.5.

B.3.1.3.2.1.1. Cornea processing

The preparation of the cornea should be performed with either excision of the corneoscleral button from enucleated whole eyes in vitro or excision of the corneoscleral button from the donor eyes in situ. Preparation of cornea for lamellar keratoplasty (anterior or posterior) may

be performed using manual or automated methods. Lasers may be used to prepare corneal tissue in which unique tissue architecture is required. This can include shaping for penetrating, anterior or posterior keratoplasty.

Inspection of the endothelium is mandatory at the end of the storage period and a cell loss during storage must be taken into account, except for tissue designated for emergency or anterior lamellar grafting.

B.3.1.3.2.1.2. Sclera processing

Sclera should be prepared using aseptic techniques after removal of the corneoscleral button from the bulbus. The remaining contents (vitreous, lens, iris, choridal and retinal tissue) and adnexa (remnants of muscles, conjunctiva) should be removed. If requested the tissue should be cut into pieces.

B.3.1.3.2.2. Decontamination of tissues and cells

For decontamination of ocular tissue, antibiotics may be used in the preservation medium.

When whole eye is delivered to the eye bank, the globe should be rinsed in a disinfectant solution (e.g. povidone-iodine) and thoroughly rinsed with a balanced electrolyte solution prior to further processing for cornea and sclera preparations.

For scleral tissue, decontamination in a gentamicin bath for 20 minutes before storage in glycerin, or a quarantine period in ethanol 70% for 14 days before renewal of the ethanol 70% is recommended.

B.3.1.4. Quality control

The quality control tests on corneal grafts should consider at least the following minimum quality criteria:

- a) Endothelial characteristics (cell density and morphology);
- b) Morphology and integrity of the cornea layers;
- c) Free visual area and diameter of corneal button;
- d) No evidence of microbiological growth or malignant cells.

See generic requirements in section A.5.1.4.

B.3.1.4.1. Microbiological control

B.3.1.4.1.1. General Principle

See generic requirements in section A.5.1.4.1

Additionally, antimicrobial effects of antibiotics in the culture medium / preservation solution should be taken into account while choosing and validating the microbiological test method.

B.3.1.4.1.2. Methods

B.3.1.4.1.2.1. Microbiological controls for organ cultured corneas

During preservation in organ culture at least one sterility test of the culture medium surrounding the donor cornea is to be performed. For this purpose, a sensitive microbiological method to detect bacteria and fungi is to be applied. The test should be performed several days into the storage period, and / or at a point near distribution of the cornea e.g. at the time of terminal evaluation and transfer of the cornea into transport medium. The medium sample should not be collected for microbiological testing any earlier than on the third day of preservation, due to the known fact that donor corneas are not sterile and a significant growth of microorganisms should be awaited. Any positive microbiological culture should have the organism identified to at least the genus level.

The culture medium is to be regularly inspected for cloudiness, which may indicate contamination. If visible cloudiness or decolouration of the culture medium should occur, suitable microbiological testing should be initiated.

All used media should be stored at +31°C for four (4) weeks after transplantation of the donor cornea and inspected regularly for cloudiness. In the case of suspected contamination, suitable microbiological testing should be initiated immediately. Alternatively, the remaining culture medium may be tested for bacterial and fungal contamination readily after the tissue has been removed from the container. Further, the transplanting organization should be informed immediately to allow a short-term control examination and treatment of the recipient, if necessary. Only donor corneas without indication of contamination of the culture medium showing at least one normal finding of a sensitive microbiological test may be released for application in humans.

Instructions for surgeons to perform a microbiological test of either the donor tissue remaining after corneal trephination (i.e. the ‘donor rim’) and / or of the storage medium in which the cornea is received, is also recommended. If either of these tests are performed, the eye bank may request the results to be reported to them by the surgeon and be retained as part of the records for that tissue. Eye banks should request positive results in cases of post-operative infection that are, in the opinion of the surgeon, likely to be attributable to the donor tissue to be reported to the Eye Bank as an adverse reaction.

B.3.3.4.1.2.2. Microbiological controls for corneas in hypothermic storage

In hypothermic storage (short-time culture), a microbiological diagnosis of the culture medium is not feasible for several reasons and therefore does not have to be made. However, for such donor corneas, documented recommendation from the cornea bank to the transplanting organization is required to apply a sensitive microbiological method for detection of bacteria and fungi in the culture medium and in the remaining tissue at the time of transplantation.

B.3.1.4.1.2.3. Microbiological controls for sclera

A sensitive microbiological method to detect bacteria and fungi is to be applied for scleral tissue before storage.

B.3.1.4.2. Other controls

B.3.1.4.2.1. Other controls for cornea

The cornea should be examined both macroscopically as well as microscopically. To be able to select the tissue for the specific surgical use for which it is intended, it is necessary to check the condition of the epithelium (intended use: penetrating keratoplasty / full-thickness graft, superficial or deep anterior lamellar graft, limbal graft), the corneal stroma (intended use: penetrating keratoplasty / full-thickness graft, superficial or deep anterior lamellar graft) whose transparency is crucial; and the endothelium, which is essential for maintaining corneal transparency (intended use: penetrating keratoplasty / full-thickness graft, posterior lamellar graft).

B.3.1.4.2.1.1. Macroscopic evaluation of corneal quality

Corneal evaluation should begin with a gross optically unaided examination *in situ* where the cornea is to be inspected for transparency, epithelial defects, foreign objects, contamination and scleral colour e.g. jaundice and corneal pathology. This examination may be aided by use of a penlight or portable slit-lamp. Careful *in situ* examination is especially important for corneoscleral rim excisions *in situ* since this is the only opportunity (other than a good medical history) to determine if there are any congenital abnormalities of the anterior chamber, iris or lens or if there has been previous anterior segment surgery such as cataract surgery and lens implantation.

B.3.1.4.2.1.2.Slit lamp evaluation of corneal quality

In the process of donor cornea preservation, a slit lamp examination to exclude any visible epithelial, stromal and endothelial pathological changes (scars, oedema, significant arcus, striae, epithelial defects, endothelial guttae or disease, polymegathism, pleomorphism, infiltrates or foreign bodies) is highly recommended, but not mandatory. The slit-lamp enables a more accurate observation of the cornea, revealing earlier stages of pathology that are visible grossly. For slit lamp examination, the eye or cornea should be allowed to reach room temperature. This makes the endothelium easier to visualize and more normal in appearance.

With slit lamp, the cornea and limbal area should be inspected for features which may preclude use of tissue e.g. signs of corneal pathology or post mortem artefacts. The epithelium should be inspected for integrity and overall condition specifically abrasions, defects and foreign bodies. The stroma should be examined for overall clarity, amount of oedema and stromal folding.

B.3.1.4.2.1.3.Microscopic evaluation of corneal quality

The condition of the corneal endothelium is crucial to evaluating the suitability of corneal tissue for penetrating keratoplasty, as it is primarily the layer responsible for the maintenance of corneal hydration and transparency. During preservation, a microscopic examination (e.g. specular microscopy, phase contrast microscopy, transmitted light microscopy) of the endothelial cell layer is to be performed at least once. In the case of organ-cultivated dehydrated donor corneas this should be done shortly before the planned transplantation.

Endothelial cell examination and evaluation is not required for those corneas intended to be used only for anterior lamellar procedures.

Evaluation should include an assessment of endothelial cell morphology (pleomorphism, polymegathism) and determination of endothelial cell density. In this examination the total endothelial area is to be analysed according to a validated and regularly checked method, either counting directly with the help of a graticule or afterwards on a photograph or with a calibrated software programme. Cell counting should be done at different areas, centrally and paracentrally up to 5-6 mm from the centre.

For ease of cell counting with light microscopy, the endothelial cell borders are to be made visible by induction of swelling of the intercellular space with a hypotonic solution. The induction of the swelling and the swelling pattern is dependent on type of medium and time

of preservation. The use of a vital stain (e.g. trypan blue) may help to recognize dead or necrotic cells and denuded Descemet's membrane.

B.3.1.4.2.1.4. Pachymetric evaluation of corneal thickness

Eye Banks may choose to perform pachymetry and / or endothelial evaluation after lamellar or laser assisted preparation of tissue.

B.3.1.4.2.2. Evaluation of scleral quality

There are no absolute criteria for evaluation of scleral quality; however, scleral shells should be visually examined for gross defects before storage and distribution.

B.3.1.5. Packaging and labelling

See generic requirements in section A.5.1.5.

B.3.1.6. Storage/ preservation

B.3.1.6.1. General

See generic requirements in section A.6

Additionally, it must be recognized that while maximum storage times are recommended for the various methods of tissue preservation, in most cases it is preferable to transplant tissues before these maximum times are approached in order to optimize surgical outcome. Availability of tissue, clinical requirements and surgical need may determine the storage time for each individual tissue.

B.3.1.6.2. Methods of preservation and storage

Preservation/storage methods for recovered donor ocular tissue are presented in chapter B.2.3.6.

B.3.1.6.2.1. Preservation and storage of corneal tissue

For the preservation and storage of donor corneas, eye banks should adhere to the subsequent minimal storage conditions necessary to maintain the required biological properties of the donor cornea. For each kind of storage condition the maximum duration is to be specified. Among other features, when selecting the time interval, the potential deterioration of the required cell and tissue characteristics needs to be considered.

B.3.1.6.2.1.1. Organ culture of cornea

Organ cultured corneas are to be stored in a closed system at temperature between +30 and 38°C at normal room air; or in an open system (with gassing) at a temperature between +30 and 38°C at normal room air with 5% +/- 1% CO₂ addition.

Prior to transplantation, the cornea is to be transferred into a de-swelling / transport medium in order to thin it. In de-swelling / transport medium (containing an agent of osmolarity,(e.g. dextran) the cornea is to be stored in a closed system at temperature between +15 and 40°C at normal room air; or in de-swelling / transport medium (containing an agent of osmolarity, (e.g. dextran) in an open system (with gassing) at a temperature between +15 and 38°C at normal room air with 5% +/- 1% CO₂ addition.

Principally, especially during transport, storage temperatures of less than 1°C and more than 40°C must be strictly avoided, as they may affect the corneal tissue and consequently jeopardize the safety for the recipient.

The maximum recommended storage time for corneas in organ culture medium is thirty five (35) days including the storage in de-swelling / transport medium, with the latter not exceeding a period of six (6) days. For emergency transplants, a deviation from these storage periods is possible, with the periods to be reviewed by the person responsible on a case-by-case basis.

B.3.1.6.2.1.2. Hypothermic storage of cornea

Corneas for hypothermic storage / short-time culture should be stored in a closed system at normal room air at a temperature between + 1 and +10°C. The maximum period for hypothermic storage is fourteen (14) days.

B.3.1.6.2.1.3. Corneal cryopreservation

The maximum recommended storage time by corneal cryopreservation is two years. However, this may be extended upon the approval of the Medical Director and agreement with the transplanting surgeon.

B.3.1.6.2.2. Preservation and storage of scleral tissue

Sclera is used surgically as a structural tissue where viability is not important. Several methods of preserving and storing sclera, including the use of ethyl alcohol (70% or greater), sterile glycerin, or formalin in room temperature; Optisol-GS or saline with antibiotics in +4°C; and cryopreservation as freeze dried or frozen, are acceptable. Eye banks should

preserve scleral tissue using aseptic techniques, using one of these methods. A preservation and expiry date for scleral tissue should be specified.

B.3.1.6.3. Storage area

See generic requirements in section A.6

B.3.1.7. Documentation and release

B.3.1.7.1. General

See generic requirements in section A.5.1.6.1.

B.3.1.7.2. Release

Before tissues are released for transplantation, all pertinent records concerning donor screening, testing and quality control should be reviewed and found to be complete and accurate. Final release for transplantation is to be performed and signed by the person responsible. The documentation for the release of donor tissue is to demonstrate that all pertinent specifications were met, especially that all effective notification forms, pertinent medical records, processing records and test results were inspected.

B.3.1.7.2.1. Release of cornea

The eye bank should establish and document their criteria for release of tissue for transplantation, which should include (but is not limited to), the following:

- a) Full donor screening for contraindications with normal result;
- b) Negative serological or molecular biological diagnosis of the donor;
- c) Acceptable microbiological test result of the culture medium (except for hypothermic storage);
- d) No relevant, biomicroscopically detectable pathological changes (relevant changes are: stromal cloudiness located centrally and thus being optically relevant, stromal thinning located in the transplant area, unless proven to be of traumatic genesis, stromal changes of infectious genesis, Descemet's membrane detachment);
- e) Sufficient quantity, vitality and morphology of endothelial cells (deviations from the normal range are: large, central multicellular necroses and cell count of less than 2000-2200 endothelial cells per mm², distinct polymegatism, distinct pleomorphism, signs of significant cell loss during organ culture, distinct granulation / vacuolization, guttae in the endothelial cell layer or cornea guttata);

For all corneal transplants (elective and emergency penetrating keratoplasty, elective posterior lamellar keratoplasty, elective and emergency stroma patch, tectonic keratoplasty) only a donor cornea with a central endothelial cell count of at least 2000 endothelial cells per mm² may be released.

Donor corneas with an endothelial cell count of less than 2000 endothelial cells per mm² in the final examination may be used for all corneal transplantations except for elective penetrating keratoplasty, elective posterior lamellar keratoplasty and elective penetrating limbal keratoplasty. These restricted applications in recipients are only permissible upon consent of the person applying the corneal transplant. Containers containing such corneas are to be provided with a label with an appropriate text (e.g. ‘for emergency PKP’, ‘for anterior lamellar keratoplasty only’).

Until requirements a) – e) have been met, the donor cornea should be under quarantine. In this respect, the quarantine period for organ cultivated donor corneas should not be shorter than ten (10) days, since the valid result of a sensitive microbiological test method is not to be expected any earlier. Deviations from the quarantine period are possible as an exception, under the precondition that all above requirements are met, if the corneal transplant is needed for a case of urgent medical emergency.

B.3.1.7.2.2. Release of sclera

The Eye Bank should establish and document their criteria for release of sclera for transplantation, which should include (but is not limited to), the following:

- a) Full donor screening for contraindications with normal result;
- b) Negative serological or molecular biological diagnosis of the donor;
- c) Acceptable microbiological test result of the tissue prior to storage;
- d) Sufficient scleral quality.

B.3.1.7.3. Processing file contents

See generic requirements in section A.5.1.6.3.

B.3.1.7.4. Availability for inspection

See generic requirements in section A.5.1.6.4.

B.3.1.7.5. Traceability

See generic requirements in section A.5.1.6.5.

SECTION C: SPECIFIC AMNIOTIC MEMBRANE REQUIREMENTS

C.1.DONOR SCREENING

C.1.1. ACTIVITIES

C.1.1.1.Donor detection

See generic requirements in section A.3.1.1

C.1.1.2.Donor consent

See generic requirements in section A.3.1.2.

C.1.1.3. Donor evaluation

C.1.1.3.1. General

The suitability of a specific individual for placental tissue donation should be documented and should be based on medical and social history, clinical status, physical assessment, and testing according to the generic EU GTPs (see generic requirements in section A.1.3.3.).

C.1.1.3.2. Medical evaluation

See generic requirements in section A.3.1.6.

Additionally, amniotic membrane can only be retrieved, if the donor has had a caesarean section as well as in the absence of a known infection of the physiologically almost sterile abdominal cavity or even systemic infections (sepsis). Physical evaluation is not relevant for amniotic membrane donors.

C.1.1.3.2.1. Exclusion criteria

The selection criteria for amniotic membrane donors are based on a risk analysis in relation to the use of the donor amniotic membrane. Indications for such risks are to be identified with the help of anamnesis, appropriate sources such as donor's medical files and consultation of treating physicians, biological testing, and other suitable examinations. Unless the donation is justifiable based on a documented risk evaluation performed by the responsible person, donors are to be excluded from donating, if one or more of the exclusion criteria should apply.

In addition to the exclusion criteria mentioned in A.3.1.6.5., screening of amniotic membrane donors should be conducted for at least the following disorders, which are potentially health

threatening for the recipient(s) or pose a risk to the success of the surgery, and should not be offered for surgical purposes:

Pathologies of the female genital tract or other diseases of the donor or unborn child that might be a hazard to the recipient's safety include:

- a) Significant local bacterial, viral, paracital or mycotic infection of the genital tract, especially amniotic infection syndrome;
- b) Gestational diabetes of the donor;
- c) (Known) malformation of the unborn / newborn;
- d) Premature rupture of membranes.

Individual tissue banks may have additional exclusionary criteria.

C.2.RECOVERY

C.2.1. ACTIVITIES

C.2.1.1.Access to the operating room

See generic requirements in section A.4.1.1.

C.2.1.2. Recovery

C.2.1.2.1. General

See generic requirements in section A.4.1.3.1.

C.2.1.2.2. Deceased donors

Amniotic membranes should be collected only from living donors as part of a planned caesarean section of the donor.

C.2.1.2.3. Living donors

Donor placentas are removed by medical staff at a gynaecological clinic as part of a planned caesarean section of the donor. Staff performing the retrieval is to be dressed appropriately for the kind of retrieval so as to minimize the risk of contamination of the tissue to be removed and any hazard for the performing staff. This includes due disinfection (surgical hand disinfection), sterile clothes as well as wearing sterile gloves, face mask or protective mask and surgery cap.

C.2.1.3. Processing during recovery

See generic requirements in section A.4.1.4.

C.2.1.4. Quality control

The quality control tests on amniotic membrane grafts should consider at least the following minimum quality criteria:

- a) Absence of transmissible disease agents and malignant cells;
- b) Integrity (to provide barrier function);
- c) Accurately sized pieces and clean edges.

See generic requirements in section A.5.1.4.

C.2.1.5. Packaging and labelling

See generic requirements in section A.4.1.5.

C.2.1.5.1. Primary packaging and labelling operations

See generic requirements in section A.4.1.5.1.

Following retrieval, the obtained donor placentas are to be packaged in such a way that the contamination risk is minimized. For this purpose, sterile pouches / packs are suitable.

C.2.1.5.2. Secondary packaging and labelling operations

See generic requirements in section A.4.1.5.2.

C.2.1.6. Storage and transport after recovery

See generic requirements in section A.2.3.6.

C.2.1.6.1. Storage

The donor placentas are to be stored at appropriate temperatures to maintain their characteristics and biological functions. The storage (and transport) time of donor placentas should be kept as short as possible, and a temperature of 40°C should not be exceeded.

The following minimal storage conditions necessary to maintain the required biological properties of the donor placenta / human amniotic membrane should be adhered to:

- a) Transport time of the placenta from the operating room (OR) to the tissue bank less than 1 hour: temperature of 2-40 °C to be maintained;
- b) Transport time of the placenta from the OR to the tissue bank - 1-48 hours: transport at an appropriate environmental temperature to ensure tissue safety / stability, e.g. by use of cooling elements;
- c) Placenta storage until earliest preparation: temperature of +2-10°C to be maintained, e.g. in the refrigerator, in which case preparation should be carried out no later than six (6) hours after retrieval;

- d) Placenta storage until earliest preparation: temperature -75°C to -85°C to be maintained (in freezer), in which case preparation should be carried out no later than six (6) months after retrieval.

C.2.1.6.2. Transport

The donor placental tissues are to be transported at appropriate temperatures to maintain their characteristics and biological functions. Principally these temperatures correspond to the storage temperatures (see chapter C.2.1.6.1.).

The package and the mode of transport are to be chosen in a way as to ensure maintenance of the tissue-specific storage temperatures (see chapter C.2.1.6.1). This is to be monitored by the tissue bank at regular intervals. If temperature stability should not be reliably guaranteed by the pack or mode of transport used, also in cases of unexpectedly high or low environmental temperatures, a temperature recording unit is to be enclosed that is to measure the temperature inside the pack in minimally half-hour intervals and the data saved. In addition, the pack is to prevent contamination by persons in charge of tissue packaging and transport.

The transport time of donor placentas should be kept as short as possible.

C.2.1.7. Documentation and release for processing

See generic requirements in section A.4.1.7.

C.3.PROCESSING

C.3.1. ACTIVITIES

C.3.1.1. Reception

See generic requirements in section A.5.1.5.

C.3.1.2. Access to the processing facilities

See generic requirements in section A.5.1.2.

C.3.1.3. Processing

C.3.1.3.1. General

See generic requirements in section A.5.1.3.

C.3.1.3.2. Processing methods

See generic requirements in section A.5.1.3.2

Proof is required that the validated procedures are performed by the tissue bank staff in a uniform manner in accordance with the approved standard operating procedures.

The amniotic membrane should be processed in a sterile manner under laminar air flow. The whole placenta should be rinsed several times and the amnion and chorion should be mechanically separated according to a documented standard operating protocol. The amnion should be placed on a suitable carrier membrane (e.g. nitrocellulose membrane) and divided into smaller pieces.

C.3.1.3.2.1. Organ culture and cell culture

Not applicable for placental tissue.

C.3.1.3.2.2. Decontamination of tissues and cells

Amniotic membrane may be decontaminated using antibiotics during processing and storage.

C.3.1.3.2.3. Sterilization/disinfection of tissue

Freeze-dried amniotic membrane may be sterilized by radiation.

C.3.1.3.2.4. Viral inactivation

C.3.1.3.2.5. Prion inactivation

C.3.1.3.2.6. Other processes

C.3.1.3.3. Cross contamination

See generic requirements in section A.5.1.3.3.

To keep the contamination risk including cross contamination between individual donors as low as possible, appropriate measures are to be taken. They also include the potential risk of tissue contamination with a transmittable disease by infected staff.

Principally, contamination is possible through contact with surfaces of the retrieval and processing areas, via the staff, via material and via contact to other donor material.

Direct contact of the donor tissue and a person must be avoided. For this reason, manipulations are principally made using instruments avoiding contact of the person performing the manipulation with the part getting into contact with the tissue. All materials and surfaces coming into contact with the tissue must be sterile. The process steps and material used are to be designed in such a way that cross contamination is avoided.

The methods for discarding donor tissue are to avoid any contamination of other donor tissue, processing environment and staff.

C.3.1.4. Quality control

C.3.1.4.1. Microbiological control

During preservation of placental tissue at least one sterility test of a placenta sample stored in preservative is to be performed. It is also recommended to collect samples of different rinsing solutions and pieces of tissue for microbiological testing. In these tests, a sensitive microbiological method for detection of bacteria and fungi is to be applied.

C.3.1.4.2. Other controls

Within the frame of retrieval and preservation of human amniotic membrane, a reliable macroscopic examination of the donor placenta to exclude visible pathological changes is to be performed.

C.3.1.5. Packaging and labelling

See generic requirements in section A.5.1.5.

C.3.1.6. Storage / preservation

See generic requirements in section A.6.

C.3.1.6.1. General

See generic requirements in section A.6.1.

C.3.1.6.2. Methods of preservation and storage

For each kind of storage condition the maximum storage duration is to be specified. Among other features, when selecting the time interval, the potential deterioration of the required cell and tissue characteristics needs to be considered.

C.3.1.6.2.1. Preservation and storage at +37°C

Not applicable for amniotic membrane preservation.

C.3.1.6.2.2. Preservation and storage at +4°C

Not applicable for amniotic membrane preservation.

C.3.1.6.2.3. Cryopreservation

Amniotic membrane should be stored in sterile organ culture medium or sterile glycerol in a freezer at -75°C to -85°C or in liquid nitrogen, vapour phase. The function of the preservative is to ensure the quality and safety of the human amniotic membrane.

Principally, storage / transport temperatures of cryopreserved human amniotic membrane above -60°C are to be strictly avoided to ensure the stability of the product and maximum safety for the recipient. The tissue bank is to ensure that all storage processes are performed under controlled conditions.

A preservation and expiry date for amniotic tissue should be indicated. For cryopreserved human amniotic membrane, a total period of twelve (12) months is applicable.

Additionally, for the distribution of cryopreserved human amniotic membrane, tissue banks should adhere to the subsequent minimal transport conditions necessary to maintain the required membrane's biological properties:

- a) Transport of human amniotic membrane, within 10 minutes to the OR: at room temperature;
- b) Transport of human amniotic membrane, to be given to a third party or with a transport time of more than 10 minutes: temperatures between -60°C and -85°C to be maintained, e.g. using dry ice.

Principally, transport temperatures of cryopreserved human amniotic membrane above -60°C are to be strictly avoided to ensure the stability of the product and maximum safety for the recipient. The tissue bank is to ensure that all storage processes are performed under controlled conditions.

Freeze dried amniotic membranes should be transported at ambient temperature.

C.3.1.6.2.4. Glycerolization

See chapter 3.3.6.2.3.

C.3.1.6.2.5. Freeze drying and dehydration

Freeze dried amniotic membranes should be stored at room temperature.

C.3.1.6.2.6. Other methods of preservation and storage

Not applicable for amniotic membrane preservation.

C.3.1.6.3. Storage area

See generic requirements in section A.3.3.6.3.

C.3.1.7. Documentation and release

C.3.1.7.1. General

See generic requirements in section A.5.1.6.1.

C.3.1.7.2. Release

See generic requirements in section A.5.1.6.2.

Additionally, it must be ensured that the human amniotic membrane cannot be released by the person responsible before the below requirements have been met:

- a) Full donor screening for contraindications with normal result;
- b) Negative serological or molecular biology diagnosis of the donor shortly before and six (6) months after the donation. If initially tests for HIV 1/2 and HBC and HCV using nucleic acid amplification methods are performed in addition to the required serological tests, repeated testing after six (6) months is not required;
- c) Negative microbiological test result of one tissue sample in preservation medium per placenta;
- d) No relevant, macroscopically detectable, pathological changes in the tissue to be transplanted.

As long as these requirements have not been met, the human amniotic membrane is quarantined. The applicable quarantine period should be six (6) months or more, unless initially HIV1/2 and HBV and HCV testing was performed using the nucleic acid amplification method in addition to the required serological tests. In such cases, quarantine is required until all serological and molecular biology test results are available.

C.3.1.7.3. Processing file contents

See generic requirements in section A.5.1.6.3.

C.3.1.7.4. Availability for inspection

See generic requirements in section A.5.1.6.4.

C.3.1.7.5. Traceability

See generic requirements in section A.5.1.6.5.

SECTION D: SPECIFIC SKIN REQUIREMENTS

D.1. DONOR SCREENING

D.1.1. ACTIVITIES

D.1.1.1.Donor detection

See generic requirements in section A.3.1.1.

D.1.1.2.Donor consent

See generic requirements in section A.3.1.2.

Before medical screening and removal of tissue, informed consent must be obtained from the donor or family.

The family of the donor must be informed of the following:

- a) Use of the tissue, for therapy or for research, for further processing into ATMPs;
- b) The possibility to be informed of the results of the screening (e.g. serology test results);
- c) The possibility to be informed the tissue was transplanted or not;
- d) Medical confidentiality;
- e) The use of personal data.

D.1.1.3. Donor evaluation

D.1.1.3.1.General

See generic requirements in section A.3.1.6.1.

D.1.1.3.2. Medical evaluation

Background for personnel responsible for final donor acceptance: medical doctor.

First screenings: trained nurses as minimum.

The TE must have a procedure to update the selection criteria.

Annual review of the donor selection criteria, review of the literature, state of the art (scientific) this can also be in the Generic GTP.

Skin allografts are generally obtained from non-living donors (heart-beating or non-heart-beating donor).

The use of skin allografts for children obtained from their parents and family members is not undertaken. This practice does not necessarily increase the bio-security and results in an unnecessary medical risk with regard to the donor as well as an unnecessary cost to society.

D.1.1.3.2.1. Anamnesis

See generic requirements in section A.3.1.6.

D.1.1.3.2.2. Social evaluation

See generic requirements in section A.3.1.6.3

D.1.1.3.2.3. Physical evaluation

The donor must be inspected before starting the recovery to check the above described contra-indications. The results must be recorded and taken into account in the final release procedure of the tissue.

D.1.1.3.2.4. Exclusion criteria

The list of selection criteria for donors is based on a risk analysis related to the use of the tissue on patients; i.e. to minimize the risk of transfer of diseases for the recipient and to ensure the appropriate quality of the skin for optimal functional results.

Contra-indications specific for skin:

- a) Systemic corticoids > 20 mg/day prednisolone or equivalent for more than one episode of > 3 weeks in the past 2 years;
- b) Auto-immune dermatoses;
- c) Systemic connective tissue diseases;
- d) Diseases affecting the dermis (dermal mucinosis, nephrogenic fibrosing dermopathy, porphyria);
- e) Mechanical or microbial damage to the skin;
- f) Burns at the location on the body to be recovered;
- g) Toxicity of the skin as a result of the presence of toxic agents or poisons;
- h) Presence of possible melanomas;
- i) Systemic infections which at the time of donation are not under control.

Relative contra-indications for skin, to be decided per donor case:

- a) Extensive laceration or scars;
- b) Skin diseases with extensive involvement, such as psoriasis, eczema, nodules, decubitus, ulceration, pyoderma, mycoses;
- c) Skin disorders interfering with recovery or aesthetically not acceptable for patient treatment such as extensive tattoos;

- d) Long lasting alcohol abuse with complications such as liver cirrhosis;
- e) Diabetes for > 10 years with complications;
- f) Skin disorders interfering with recovery or aesthetically not acceptable for patient treatment such as extensive tattoos;
- g) Long lasting alcohol abuse with complications such as liver cirrhosis;
- h) Diabetes for > 10 years with complications.

Age limits: Minimum: 18 - Maximum: none

D.1.1.3.2.5. Post Mortem Time

Maximum period of time permitted before recovery of the tissue.

The skin should be procured as quickly as possible after death. Should the donor not be refrigerated after dying, then recovery should be completed within 12 hours of death. Should the donor be refrigerated within six hours of dying, then the recovery of the skin should be completed within 48 hours of death. In this case, blood samples for laboratory screening should be collected and processed within 24 hours of death. Pre-mortem blood samples can also be used, when available. It is recommended, however, that even when refrigeration has been implemented recovery should be started within 24 hours of the donor's death.

Blood tubes should be centrifuged as soon as possible after withdrawal to separate the cells from the serum or plasma so as to avoid false positive or negative results. It is advisable to use tubes with a gel clot. If possible, the tubes should be centrifuged at the recovery site to check the quality of the samples immediately so another sample can be drawn or pre-mortem samples can be obtained from the hospital laboratory.

D.1.1.3.2.6. Laboratory test results

Blood samples must be taken just prior to death or within 24h after death.

- a) HIV 1 and 2
- b) HCV
- c) HBV (HbsAg and anti-HBc)
- d) HTLV II/I for donors from areas with high incidence
- e) TPHA
- f) For HIV and HCV: NAT testing

In case the information is needed:

- a) ABO group;
- b) Rhesus factor;
- c) Result of CMV serology;

D.2. RECOVERY

D.2.1. ACTIVITIES

D.2.1.1. Access to the operating room

See generic requirements in section A.4.1.1.

D.2.1.2. Recovery

D.2.1.2.1. General

See generic requirements in section A.4.1.3.1.

D.2.1.2.2. Recovery

The recovery procedures are such that the properties of the tissues, which are important for the ultimate clinical use, are preserved and that microbiological contamination is avoided as far as possible during the process

D.2.1.2.2.1. Donor identification

See generic requirements in section A.3.1.1.2

D.2.1.2.2.2. Gowning

See generic requirements in section A.4.

D.2.1.2.2.3. Donor preparation

The skin is removed making use of aseptic techniques. Before recovery, the skin should be treated with a suitable anti-bacterial agent. When selecting this agent a reasonable compromise must be found between loss of viability (viability is important in certain clinical applications) and the efficiency of the decontamination process.

Partial thickness skin can be taken of using a dermatome that can be adjusted to the appropriate thickness in such way intact skin is recovered. Thickness may range from 0.2 mm- 1.0 mm. Full thickness skin can be recovered using a scalpel.

D.2.1.3. Reconstruction of the donor

For aesthetic reasons and with a view to a respectful reconstruction of the donor, it is not acceptable to take skin from the neck, face and other places which would be visible when people pay their last respects to the donor.

Bearing in mind that (partial) removal of skin is always accompanied by a considerable loss of fluid over time, the necessary measures should be taken to prevent this loss or else ensure this is not noticeable when people are paying their last respects to the donor.

D.2.1.4. Quality control

Pre-processing samples for microbiology tests can be taken, depending on the type of processing method.

D.2.1.5. Packaging and labelling

See generic requirements in section A.4.1.5.

D.2.1.5.1. Primary packaging and labelling

The recovered skin is transferred to sterile container (s). After closure, a label with the unique donor identification number indicating that the tissue is not released for transplantation.

D.2.1.6. Storage and transport after recovery

See generic requirements in section A.4.1.6.

D.2.1.6.1. Transport after tissue recovery

Recovered skin must be transported in a suitable medium. This transport medium may contain one or more antibiotics so that immediately after recovery microbial inactivation can be started with (at the point recovery takes place the skin is not sterile). When making the choice of a transport medium, the choice of antibiotics and temperature at which the skin will be transported, a reasonable compromise should be found between the loss of function, viability (viability is important in certain clinical applications) and the efficacy of the decontamination. The transport should be validated and should not cause the skin to become clinically ineffective or harmful for the recipient. Should microbial inactivation be implemented then this procedure should be specified (in the standard practice conditions of the skin bank), documented, validated and be reported to the surgeon carrying out the transplantation.

Upon receipt of the container containing the donor material, checks will be carried out to establish if any leakage has occurred during transportation or whether any damage or breakage has been suffered by the container and/or if the seal of the top has been broken. The refrigeration process must at no time be interrupted, depending on the requirements of the processing method that will be used for the skin. In addition the labels will be examined to see if they are intact and legible. Each of the above mentioned situations would provide reason for the tissue being rejected.

D.2.1.7. Documentation and release for processing

See generic requirements in section A.4.1.7

D.3. PROCESSING

D.3.1. ACTIVITIES

D.3.1.1. Reception

See generic requirements in section A.5.1.5.

The recovered skin should be transferred to the tissue establishment as soon as possible after recovery or must be put in the first processing fluid direct after recovery. After the skin has been received at the tissue establishment the processing of the skin should commence within 72 hours of recovery having taken place. In expectation of the processing, the skin should be kept at 2-8°C, in a physiological medium with sufficient buffering capacity.

D.3.1.2. Access to the processing facilities

See generic requirements in section A.5.1.2.

D.3.1.3. Processing

D.3.1.3.1. General

See generic requirements in section A.5.1.3.

The recovered skin is processed to allow longer storage periods until transplantation in suitable patients. The methods used must be validated and must kept up with the scientific state-of-the-art in due time.

Critical processing procedures must be validated and may not inactivate human tissues and cells, or make them harmful to the recipient. This validation can be on the basis of studies undertaken by institutions themselves, on details of published studies or, where accepted processing procedures are concerned, retrospective evaluation of clinical results achieved with human tissues and cells provided by the establishment.

D.3.1.3.2. Processing methods

D.3.1.3.2.1. Processing of tissues

Unsuitable pieces of skin are cut away and irregular edges trimmed after which the remaining section can be measured in order to calculate the surface area of the skin allograft in question. The dimensions of the skin allograft are expressed in square centimetres (cm²).

D.3.1.3.2.2. Decontamination of tissues

Unsuitable pieces of skin are cut away and irregular edges trimmed after which the remaining section can be measured in order to calculate the surface area of the skin allograft in question. The dimensions of the skin allograft are expressed in square centimetres (cm^2).

D.3.1.3.2.3. Sterilisation of tissues

Whether or not the skin may be sterilised is dependent on the clinical application and the quality requirement set. Conventional sterilisation methods (for example radiation, heat, gas and immersion in chemical agents) have a detrimental effect on the structural integrity and viability of the skin.

D.3.1.3.2.4. Inactivation with regard to prions

Specific inactivation with regard to prions is possible if the viability of the skin allograft is not a prerequisite for the intended clinical use. In all other cases all the products used that constitute a risk should be accompanied by the necessary certificates in order to reduce the risk to a minimum.

D.3.1.4. Quality control

The quality control tests on skin grafts should consider at least the following minimum quality criteria:

- a) Absence of transmissible disease agents and malignant cells;
- b) Correct thickness;
- c) Integrity (to provide barrier function);
- d) Accurately sized pieces and clean edges;
- e) Cell viability (optional, depending on the intended application);
- f) Sterile if labelled as such.

See generic requirements in section A.5.1.4.

D.3.1.4.1. Microbiological control

D.3.1.4.1.1. General principle

See generic requirements in section A.5.1.4.1.

D.3.1.4.1.2. Microbiological controls

1. Skin is an inherently non-sterile tissue and is also not sterile at the time of recovery. This makes it a complex matter to draw up standards that are functionally achievable and ethically responsible within the framework of the tissue transplant standards.

2. With the bacteriological and mycological evaluation of the skin allografts every effort must be made to ensure the absence of relevant pathogens (Table 1 and others) and to determine an appropriate threshold of asepticism (bio burden).
3. Pathogens may at no time be allowed to occur on skin allografts, irrespective of their density. The bacteriological and mycological investigations may however reveal the presence of low density micro-organisms, which form a part of the inherent resident skin flora.
4. Sampling making use of a swab is not permitted. A correlation exists between the positive culture and the quantity of skin used. The taking of representative samples (\pm of a minimum 2 cm²) is thus indispensable.
5. All processes are carried out on representative samples in accordance with standard clinical-microbiological techniques over a period of 14 days (this is still in discussion in Belgium, 7 days may be also appropriate). The samples are cultured in an appropriate fluid enrichment media for aerobic and anaerobic bacteria, yeasts and fungi and any growth in the medium is monitored on a daily basis. Should growth be observed (turns opaque/murky, turbid) within 7 days then the tissue is rejected. Should the growth be observed after day 7, then the micro-organisms should be identified according to standard clinical-microbiological techniques. The tissue is rejected when pathogenic germs are identified.
6. The choice for this culture media and the protocol for the microbiological tests fall under the auspices and responsibility of the recognised laboratory to which the tissue establishment sends the samples to be tested.
7. Should antibiotics, or other products with an antimicrobial action, be made use of in the transportation and/or conditioning process, then these should be removed (for example by copious rinsing) or inactivated prior to the bacteriological and mycological inspections. Validated protocols concerning the rinsing or inactivation processes must be in place at the tissue establishment.
8. Hemocultures have value as a source of information but have more than likely no added value with respect to the quality and safety of the skin allografts.

Table 1. Germs that definitely must not occur on skin allografts

Acinetobacter baumannii
Beta-hemolytic streptococci
Burkholderia cepacia
Clostridium perfringens
Clostridium tetani
Corynebacterium diphtheriae
Enterobacteriaceae (coliforms)
Pseudomonas aeruginosa
Staphylococcus aureus (MRSA/MSSA)
Aspergillus spp.
Candida spp.
Mucor spp.
Penicillium spp.
Other yeasts and fungi
Mycobacteria (in an ‘at risk donor’)

Table 2. Summary

Incubation period for skin samples	
1 to 7 days inclusive	8 to 14 days inclusive
Growth ➔ tissue rejected	Presence of commensal flora only ➔ tissue approved
	Presence of a pathogen ➔ tissue rejected

9. In order to detect fungal growth on the skin allografts it is sufficient for the sample to be cultured for 14 days. If the tissue does not meet the above stated conditions, validated bacterial inactivation is acceptable.

D.3.1.5. Packaging and labelling

See generic requirements in section A.5.1.5.

D.3.1.5.1. Primary packaging and labelling

The primary packaging (the packaging that comes into contact with the skin allografts) should be suitable for this purpose (if available, medical device class IIa packaging).

In order to offer extra protection to the skin allograft it is preferable that an additional secondary packaging is utilised.

D.3.1.6. Storage/ preservation

D.3.1.6.1. General

See generic requirements in section A.6.

D.3.1.6.2. Methods of preservation and storage

Depending on the clinical application and the quality requirement stipulated, skin can be preserved in a number of different ways. Cryopreservation in liquid nitrogen and/or glycerolisation are the methods normally used. Cyopreserved or glycerolised skin is used as ‘biological dressing’ for temporary coverage of (burn) wounds. Compared to the other tissues such as heart valves or cornea, the donor skin is present much shorter in the patient’s body when used as biological dressing.

Skin can also made acellular in order to use it as dermal implant; for instance in the Cuono method or under an autologous very thin split skin to reduce donor site morbidity on the patient and achieve a better scar quality. In this type of treatment, the donor skin is gradually remodelled and replaced by the patient’s own tissue within a couple of months.

Every preservation and storage process should be specified (in the standard operating procedures of the tissue establishment), documented and validated.

Each type of storage condition should specify the maximum shelf life. This would include, among other matters, taking into account any deterioration in the required properties of the skin. This maximum shelf life should be documented and validated and reported to the surgeon carrying out the transplantation. Regular critical evaluation of the preservation method used by the TE must be carried out to ensure that the intended results are still achieved. Prior to the implementation of a significant process change the altered method has to be validated and documented.

D.3.1.6.2.1. Preservation and storage at 37°C

This method used fluids with antibiotics and nutrients to keep the cells in the skin viable. This method can be used for a short period, 2-3 days.

D.3.1.6.2.2. Preservation and storage at +4°C

This is a method for storage viable skin allografts, maintaining their structural integrity, for short periods of time (days to weeks). A physiological preservation medium with nutrients and possessing sufficient buffering capacity is recommended.

D.3.1.6.2.3. Cryopreservation at between -60°C and -80°C

This is a method for preserving viable skin allografts, maintaining their structural integrity, for medium term periods (months). A controlled (refrigeration curve) and validated refrigeration procedure is recommended.

D.3.1.6.2.4. Cryopreservation in liquid nitrogen

This is a method for preserving viable skin allografts, maintaining their structural integrity, for longer periods (years). A controlled (refrigeration curve) and validated refrigeration procedure is recommended. The skin allografts are stored in liquid nitrogen (gases) at a temperature below -130°C.

D.3.1.6.2.5. Glycerolisation with a high glycerol concentration

This is a method for preserving non-viable skin allografts. Glycerol concentrations of between 85 and 98% are the norm. The glycerol concentration is increased in a gradual manner. The glycerol solutions used are preferably of Ph. EU quality but at least from vegetable origin.

Glycerol has an anti-microbial action and will result in the skin being less immunogenic. Glycerolised skin allografts should be kept at 2 to 8°C.

D.3.1.6.2.6. Lyophilisation and dehydration

Rarely used and quite roundabout methods for storage non-viable skin allografts. Lyophilised skin can be kept at room temperature.

D.3.1.6.2.7. Decellularisation

These are methods to lower the antigenicity of the skin further compared to glycerolisation. Removing the donor cells can be done by incubation of the skin in high concentration on NaCl (<1 M) or low concentrations of NaOH

D.3.1.6.2.8. Other preservation and storage procedures

A number of other procedures for the preserving and storage of skin allografts have been described in academic journals. These include:

- a) Vitrification;
- b) Preservation in high concentrations of propylene glycol;
- c) Preservation at 22°C in anhydrous NaCl (sodium chloride).

D.3.1.6.3. Storage area

See generic requirements in section A.6.

D.3.1.7. Documentation and release

D.3.1.7.1. General

See generic requirements in section A.3.3.7.1.

D.3.1.7.2. Processing file contents

See generic requirements in section A.5.1.6.3.

D.3.1.7.3. Availability for inspection

See generic requirements in section A.5.1.6.4.

D.3.1.7.4. Traceability

See generic requirements in section A.5.1.6.5.

SECTION E: SPECIFIC CARDIOVASCULAR REQUIREMENTS

E.1 DONOR SCREENING

E.1.3. ACTIVITIES

E.1.3.1.Donor detection

See generic requirements in section A.1.3.1

E.1.3.2.Donor consent

See generic requirements in section A.1.3.2

E.1.3.3. Donor evaluation

E.1.3.3.1.General

E.1.3.3.2. Medical evaluation

See generic requirements in section A.1.3.3.2.

E.1.3.3.2.1.Anamnesis

See generic requirements in section A.1.3.3.2.1

E.1.3.3.2.2.Social evaluation

See generic requirements in section A.1.3.3.2.2

E.1.3.3.2.3.Exclusion criteria

- a) Cardiac valvulopathy of the aortic and pulmonary valves, with incontinence from moderate to severe
- b) Chronic alcoholism
- c) Important smoking
- d) Age over 65 years
- e) Anorexia and bulimia
- f) Aortic dissection
- g) Direct and massive traumas in the recovery area
- h) Down's, Marfan's or Doonan's syndrome
- i) Epilepsy ascertained and in therapy
- j) Exposure to temperature $\leq 0^{\circ}\text{C}$
- k) Pneumonia in the 30 previous days without evidence of resolution
- l) Previous cardiosurgical interventions on the cardiac valves or vascular segments to recover

- m) Bacterial or fungal endocarditis
- n) Diabetes mellitus
- o) Hyperlipidemia
- p) Viral myocarditis

E.1.3.3.2.4.Donor age

60 years for men and 65 for women is advisable

E.2. RECOVERY

E.2.1. ACTIVITIES

E.2.1.1. Access to the operating room

See generic requirements in section A.2.3.1.

E.2.1.2. Recovery

See generic requirements in section A.2.3.2

The delay of recovery must be always as short as possible.

The maximum delay for the vascular tissue recovery in case of the non heart-beating donor is 24 hours with the condition that the warm ischemia time (delay between death and the beginning of cooling) is not longer than 6 hours.

E.2.1.2.1. Recovery

E.2.1.2.1.1. Donor identification

The unique identification code of tissues and cells is attributed by the bank and should be based on national or European coding system

E.2.1.2.1.2. Gowning

See generic requirements in section B.2.1.2.2.2.

E.2.1.2.1.3. Donor preparation

The following particular specific aspects of the arterial and / or venous vessels to be recovered for vascular allograft preparation are:

- a) Maintain the maximal length of the recovered vessel;
- b) Collateral branches are cut at 2-3mm from the arterial wall. They may not be clipped cut by the metallic clips;

- c) Avoid causing iatrogenic lesions during the manipulation; the veins during the stripping procedure may be accepted for allograft preparation with the condition they are meticulously examined.

E.2.1.2.1.4. Living Donors

For living donor: in the case of a patient undergoing a heart transplant, if the heart to be replaced has no valvular lesions, it can be recovered for valves.

E.2.1.3. Processing during recovery

See generic requirements in section A.2.3.3.

E.2.1.4. Quality control

E.2.1.5. Packaging and labelling

See generic requirements in section A.2.3.5.

The recovered tissues are placed in the crystalloid transport solution(e.g. NaCl 0.9%, Ringers lactate, HTK, Medium 199), with the possible addition of nutritional or osmotic elements (Betzler, Hank's medium, albumin, ...) and packaged separately in three sterile packaging layers ('pouches') after recovery. Each tissue / organ must be labelled and identified by a specific internal code.

This package is then placed in another container ensuring a temperature between +2°/+10°C and the protection of the recovered tissues during transport. It is essential that the container is closed correctly and is not opened again until its reception in the tissue establishment

E.2.1.6.1. Storage after tissue recovery

Vessels and valves must be maintained at + 2/+10 ° C until the preparation phase, which should be carried out within 12 hours (maximum 24 hours) after the arrival at the bank. Tissues are prepared according to normal surgical procedures for isolation of the heart valves and vascular segments.

E.2.1.6.2. Transport after tissue recovery

This package is then placed in the container which ensures the temperature between 0 and 4°C (filled with the wet ice) as well as the physical protection of the recovered material during transport. It is essential that the container is closed correctly and is not opened again until its reception in the tissues and cells bank, where it is to be processed.

E.2.1.7. Documentation and release for processing

See generic requirements in section A.2.3.7.

E.3. PROCESSING

E.3.1. ACTIVITIES

E.3.1.1. Reception

See generic requirements in section A.3.3.1.

Information required concerning the donor and the acquisition of human material:

- a) Donor identification. The unique identification code of tissues and cells is attributed by the bank of tissues and cells or a national/international system;
- b) Donor sex and age;
- c) Donor type: living (domino)donor, deceased heart-beating organ donors, deceased non heart-beating (organ)donor, cadaveric (tissue) donor;
- d) Informed consent (living donors): a copy of the original or signed consent result of the consultation of the national register;
- e) Identification of the recovery centre and the responsible person of donation and recovery;
- f) Personal medical history of the donor (absence of the exclusion criteria);
- g) Cause of death;
- h) Results of the clinical examination and autopsy in relevant cases ;
- i) Date and time of circulatory arrest (for deceased donors) ;
- j) Date and time of cooling of the body (for the non-heart beating donors);
- k) Place, date and hour of the recovery ;
- l) Description and identification of the recovered material (**arteries, veins**).

E.3.1.2. Access to the processing facilities

See generic requirements in section A.3.3.2.

E.3.1.3. Processing

E.3.1.3.1.General

See generic requirements in section A.3.3.3.1.

E.3.1.3.2. Processing methods

E.3.1.3.2.1. Processing of tissues and cells

In order to avoid the complementary warm ischemia time during the processing, the tissues must remain humid and have a low temperature (if possible below 10°C).

In, order to avoid further warm ischemia during the dissection of recovered blood vessels, the tissues must remain humid and the temperatures need to be low (as low as possible, below +10°C).

E.3.1.3.2.1.1. Processing of valves

During the heart dissection, the aortic and the pulmonary roots are separated and in some cases the mitral valve as well. During this phase the morphological description, and measuring of the dissected allografts is performed, as well as functional testing of the valves.

The allograft needs to be described in detail; this description must mention all the tissue malformation and the iatrogenic lesions.

The functional tests, leaflet coaptation and level of leak, must be checked. The results of this test must be noted in the allograft record.

The heart valves are sized on the basis of the internal diameter of the valva anulus, expressed in millimetres (mm). The valve annulus may be neither distended nor distorted.

The length and the internal diameter of the arterial conduits (aortic, pulmonary trunk as well as the left and right pulmonary branches) must be mentioned as well.

GRADING

GRADE 1 (valves to be discarded):

- Unusable valve leaflet;
- Negative leaflet coaptation test;
- Conduit and valvular leaflet calcification;
- Valvular insufficiency;
- Severe damage due to dissection or recovery;
- Bicuspid congenital defects;
- Intimal injuries along the aortic conduit.

GRADE 2 (unusable valves except for monocuspid preparation):

- Abnormal valve leaflets;
- Negative leaflet coaptation test;
- Atheromas on over 30% of the valvular and conduit surface;
- Calcification areas at intimal level.

GRADE 3

Normal valve leaflet;
Positive leaflet coaptation test;
Absence of calcification and atheromas on the valve leaflets;
Mitral valve with atheromas on 15- 30% of the valve surface;
Absence of calcification on the conduit and presence of atheromas on 15-30% of the surface;
Presence of small bruising areas but not in proximity of the valvular ring.

GRADE 4

Excellent valvular leaflet;
Positive leaflet coaptation test;
No damages;
Fenestrations on <2% of the area;
Absence of calcifications and atheromas; Small atheromatous areas on <5% of the mitral valve surface;
Absence of intimal injuries of the conduit of the conduit with atheromas on <15% of the surface.

GRADE 5

Tissue and valve leaflet anatomically perfect.

E.3.3.3.2.1.2. Processing of vessels

The allograft needs to be described in detail (aspect and consistence); this description must mention all the tissue malformation and the iatrogenic lesions.

The vessels are sized on the basis of the diameter, expressed in millimetres (mm) and the length in centimetres (cm).

GRADING ARTERIAL VASCULAR TISSUE

GRADE I; (Not eligible)

Aneurysmatic tissue or presence of blisters;
Transmural diffuse calcifications (>30%);
Extensive intimal ulceration areas;
Negative pressure test.

GRADE II: (Subject to evaluation)

Megaarteries;
Fibro-calcific thickening areas;
Segmental calcific atheromas (<15%) protruding into the lumen without ulcerative lesions;
Positive pressure test;
Fenestration on >5% of the total surface.

GRADE III: (eligible) Anatomically perfect;

Little collection of fibrolipidic material;
Positive pressure test.

GRADING VENOUS VASCULAR TISSUES

GRADE I:

Varicose tissue;
Failure areas on >30% of the total surface;
Parietal fibrosis infiltrating or periavventitial areas on >15%;
Negative pressure test.

GRADE II:

Thickened segment;
Not dilated;
Some limited ectasias

GRADE III: No apparent lesions

QUALITY CODES DEFINITION LIST, VALVES:

Acceptable for further processing:

Code 01: No visible morphological abnormalities
Code 02: Minimal atheroma in basal attachment of leaflet;
Minimal fibrosis in (basal attachment of) leaflet / vascular wall;
Fenestration(s) in otherwise perfect graft;

Petechia in otherwise perfect graft.

Code 03: Minor atheroma in vascular wall (conduit);

Atheroma in < 1/3 of the basal attachment of the leaflet;

Fibrosis in < 1/3 of (the basal attachment of) the leaflet;

Fenestrations.

Code 04: Atheroma in the vascular wall;

Atheroma in < 2/3 of the basal attachment of the leaflet;

Fibrosis in < 2/3 (of the basal attachment) of the leaflet;

Fenestrations.

Code 05: Discrete atheroma in the vascular wall or the basal attachment of the leaflet;

Discrete fibrosis in (basal attachment of) leaflets;

Pinpoint calcification in vascular wall;

Minor adhesions of leaflets at the commisures;

Fenestrations.

* Codes 04 and 05 are not acceptable for aortic valves from donors \geq 56 years of age.

Not acceptable for further processing:

Code 06: Extensive fibrosis or atheroma and/or calcification in vascular wall, calcification in leaflets, Major leaflet adhesion, fenestrations $>$ 1/3 the length of free edge Rigid vascular wall (conduit) Large areas of detached intima / tears in vascular wall (conduit).

Code 07: Damaged during removal of the heart.

Code 08: Damaged during dissection of the heart.

Code 09: Incompetent valve.

Code 10: Other abnormalities (anatomical or procedural).

Code 11: Failure to meet one or more of the time limits adherence requirements detailed in SOP P-01.

QUALITY CODES DEFINITION LIST, VESSELS:

Acceptable*:

Code 01: No visible morphological abnormalities.

Code 02: Superficial atheroma, minor spots of fibrosis.

Code 03: Minor fatty streaks, minor fibrosis.

Not acceptable:

- Code 06: Discrete atheroma: patches in > 1/3 of the surface area of the vessel wall;
Calcification.
- Code 07: Damaged during removal of the aorta segment from the donor.
- Code 08: Damaged during dissection in the Bank.
- Code 10: Other abnormalities (anatomical or procedural).
- Code 11: Failure to meet any of the time limits adherence requirements detailed in SOP P-01.

EVALUATION OF VALVES

Not acceptable valves:

- Unusable valve leaflet
- Calcification and extensive fibrosis in leaflets
- Negative leaflet coaptation test (Incompetent valve)
- Valvular insufficiency
- Major leaflet adhesion
- Fenestrations > 1/3 the length of free edge
- Conduit calcification
- Intimal injuries along the aortic conduit (Large areas of detached intima / tears in vascular wall)
- Rigid vascular wall (conduit)
- Severe damage due to dissection or recovery
- Other abnormalities (anatomical or procedural) e.g. Bicuspid congenital defects;

Not acceptable vessels

- Discrete atheroma: patches in > 1/3 of the surface area of the vessel wall
- Aneurysmatic tissue or presence of blisters
- Transmural diffuse calcifications
- Extensive intimal ulceration areas;
- Aneurysmatic tissue or presence of blisters;
- Transmural diffuse calcifications
- Extensive intimal ulceration areas;
- Negative pressure test.
- Damaged during removal from the donor

Damaged during dissection in the Bank
Other abnormalities (anatomical or procedural)

E.3.1.3.2.2. Decontamination of valves and vessels

E.3.1.3.2.2.1. Decontamination of valves

Allografts are microbiologically sampled and cultured for aerobic and anaerobic germs as well as for fungi and yeasts before antibiotic incubation.

Samples on which analyses must be performed are:

- a) The transport medium at the beginning of processing
- b) Subvalvular (aortic and pulmonary) myocardial tissue
- c) End sample after decontamination and rinsing, before final packaging

Each bank should establish in its operating procedures a list of pathogens whose presence leads to the elimination of the tissue even though disinfection was successful.

Microorganisms that never be found in a cardiovascular tissue sample (pre-antibiotic or post-antibiotic sample)

Clostridium sp.
Clostridium perfringens
Clostridium tetani
Enterococcus sp
Flavobacterium meningiosepticum
Klebsiella rhinoscleromatis
Listeria monocytogenes
Neisseria gonorrhoeae
Nocardia sp.
Pseudomonas aeruginosa or pseudomallei
Staphylococcus aureus (MRSA)
Salmonella sp.
Shigella sp.
Streptococcus pyogenes (group A)
Aspergillus spp.
Candida spp.

Mucor spp.
Penicillium spp.
Other yeasts and fungi
Mycobacteria (in an “at risk donor”)

Each tissue is placed in a disinfecting solution in a sterile container labelled with a specific internal code. The composition of the solution, the incubation temperature and the duration are defined by the bank’s standard operating procedures.

The tissues shall be incubated with antibiotics during 5 to 6 hours at 37 °C. An ampoule with 2 ml of the antibiotic cocktail is transferred to a solution of Medium 199 obtaining an endvolume of 100 ml (50 times dilution).

The antibiotic cocktail consists of:

Ciprofloxacin,	0.15 mg/ml
Amikacin,	0.6 mg/ml
Metronidazole,	0.6 mg/ml
Vancomycin,	0.6 mg/ml
Flucytosine,	1.5 mg/ml

Since there are different protocols of decontamination and different temperature conditions and duration, each tissue establishment would have to be free to decide the sterilization conditions of the allografts.

E.3.1.4. Quality control

The quality control tests on cardiovascular grafts should consider at least the following minimum quality criteria:

- a) Absence of transmissible disease agents and malignant cells;
- b) Functional competence;
- c) Good morphology (no fissures, congenital defects, no/minimal calcification etc.);
- d) Anatomical suitability; accurate length of conduit and diameter of annulus;
- e) Tissue matrix structure intact;
- f) Biomechanical strength.

See generic requirements in section A.3.3.4.

E.3.1.4.1. Microbiological control

E.3.1.4.1.1. General principle

See generic requirements in section A.3.3.4.1.

E.3.1.4.1.2. Microbiological controls

E.3.1.4.1.3. Methods

E.3.1.4.2. Other controls

E.3.1.5. Packaging and labelling

See generic requirements in section A.3.3.5.

At the end of the time stipulated by the antibiotic schedule, the tissues are packaged for cryopreservation.

The cryobags used have to assure the nitrogen liquid resistance as well the isolation of the samples.

When the storage of the tissues are in liquid nitrogen two bags are mandatory in order to prevent a possible liquid nitrogen contamination if the bag breaks.

E.3.1.6. Storage/ preservation

E.3.1.6.1. General

See generic requirements in section A.3.3.6.1.

In order to assure the tissue quality, it is essential that the processing and preservation take as less time as possible, with a total ischemia time of 72 hours!

The maximum defined delays are 24 hrs for the start of recovery, 40 hrs for the start of processing and 48 hrs for the start of cryopreservation (starting from the moment of circulatory arrest in case of deceased donors). The moment of the death (or the circulatory arrest) that of recovery (in case of living donors), the beginning of processing and of the cryopreservation are indicated on the record of concerned tissue.

The processing should be performed within 24 hours of cardiac arrest/recovery and finish with cryopreservation at maximum 72 hours of cardiac arrest.

Any extension of these delays may eventually be accepted only after specific validation of the particular case.

E.3.1.6.2. Methods of preservation and storage

The standard operating procedures (SOP) describe the solutions, the duration and the temperature of incubation as well as the freezing parameters.

This information along with other information is communicated to the implanting surgeon at the moment of the allograft delivery or by means of a periodically distributed protocol.

E.3.1.6.2.1. Storage at +4°C

If the antibiotics incubation can not be directly followed by cryopreservation, the allografts may be stored at a temperature of +4°C in an appropriate solution (Medium 199) until cryopreservation (maximum is 40 hours after circulation stop). Any longer storage periods need to be subjected to thorough research to determine if the quality of the tissue is high enough to be used safely.

E.3.1.6.2.2. Cryopreservation and storage at -80°C

During the cryopreservation, the speed of the freezing with the intermediary temperature of the cryopreservation procedure (for the chamber as well as for the control tissue) must be recorded. Storage at -80°C is acceptable for a short period (maximum 1 months). Longer periods of storage at -80 °C are not acceptable.

This issue is for discussion. In the literature is mentioned that you can store up to 6 months maximally. However, the majority of TE-s are accepting actually to 3 months. For me this modification can be acceptable!

Allografts to be shipped need to be kept in dry ice, at the temperatures between -70°C and -80°C (-76°C).

The shipment and temporary storage of the vascular allograft in the dry ice at -70°C to -80°C is acceptable with the condition that the allograft remains in these (controlled) temperature conditions until use. It may not be re-stored in the initial storage temperature (-170°C or lower) and its storage duration is limited to maximum 1 month from the moment of removal from the initial storage conditions

E.3.1.6.2.3. Cryopreservation and storage in Liquid Nitrogen

Tissues are cryopreserved by using a controlled rate freezer. With a specially programmed protocol (implementing various freezing parameters) the tissues reach a temperature of -100 °C. During the cryopreservation protocol, the speed of the freezing must be recorded, as well as any consistencies that might have occurred during the freezing run. After

cryopreservation the frozen tissues are transferred to a temperature monitored liquid nitrogen tank.

Freezing must happen in controlled rate freezer, decreasing the temperature very slowly (-1°C) down to -40°C (to avoid recrystallization at the level of -23°C) and then rapidly (-5°C) down to -1000°C.

The storage in the vapour phase of liquid nitrogen (between -170°C and -190°C) (-150°C and -187°C) is acceptable for a period of 5 years.

After longer storage periods the tissues expire and need to be discarded. Another option is using these expired tissues in validated research experiments.

Thawing, removal of cryoprotection medium (dilution) and re-establishment of the isotonic state of the vascular allograft are of critical importance in order to guaranty the integrity of the cryopreserved tissue. Also, among the other information on tissues and cells, the accompanying record of the cryopreserved tissue must contain the detailed protocol of thawing and dilution, tissue reconstitution and a list of the necessary material.

E.3.1.6.3. Storage area

See generic requirements in section A.3.3.6.3.

E.3.1.7. Documentation and release

E.3.1.7.1. General

See generic requirements in section A.3.3.7.1.

E.3.1.7.2. Release

See generic requirements in section A.5.1.6.2.

E.3.1.7.3. Processing file contents

See generic requirements in section A.3.3.7.3.

E.3.1.7.4. Availability for inspection

See generic requirements in section A.3.3.7.4.

E.3.1.7.5. Traceability

See generic requirements in section A.3.3.7.5.

E.3.1.7.6. Archive

See generic requirements in section A.3.3.7.6.

SECTION F: SPECIFIC MUSCULOSKELETAL REQUIREMENTS

F.1 DONOR SCREENING

F.1.1. ACTIVITIES

Musculoskeletal tissue donors are usually deceased donors. There can be also explanted musculoskeletal tissues, e.g. femoral head accepted for donation from living donors.

F.1.1.1.Donor detection

See generic requirements in section A.3.1.1

F.1.1.2.Donor consent

See generic requirements in section A.3.1.2

F.1.1.3. Donor evaluation

F.1.1.3.1.General

1.The suitability of a specific individual for musculoskeletal tissue donation should be documented and should be based on medical and social history, clinical status, physical assessment, testing and autopsy (if performed) according to the generic EU GTPs (see generic requirements in section A.1.).

F.1.1.3.2. Medical evaluation

See generic requirements in section A.3.1.6.

F.1.3.3.2.1. Anamnesis

See generic requirements in section A.3.1.6

F.1.3.3.2.2. Social evaluation

See generic requirements in section A.3.1.6.3

F.1.3.3.2.3. Physical evaluation

1. All prospective musculoskeletal tissue donors should undergo a thorough physical examination as close as possible prior to donation with special attention to physical signs of HIV disease, infectious hepatitis, and injecting illegal drug use (see generic requirements in section A.3.1.6.4).

F.1.3.3.2.4. Exclusion criteria

1. The selection criteria for musculoskeletal tissue donors are based on a risk analysis in relation to the use of the donor tissue. Indications for such risks are to be identified with the help of anamnesis, appropriate sources such as donor's medical files and consultation of treating physicians, biological testing, post mortem examination, and other suitable examinations, e.g. autopsy results. Unless the donation is justifiable based on a documented risk evaluation performed by the responsible person, donors are to be excluded from donating, if one or more of the exclusion criteria should apply.
2. Below is presented the MINIMUM set of contraindications for use of different musculoskeletal tissue for transplant purposes. Individual musculoskeletal banks may have additional exclusionary criteria. Some criteria listed as generally exclusionary may be acceptable depending on the storage method used for tissue preservation.

F.1.3.3.2.4.1. Exclusion criteria musculoskeletal tissue donors

1. In addition to the exclusion criteria mentioned section A.3.1.6.5. of the generic GTP requirements, screening of musculoskeletal tissue donors should be conducted for the following disorders and age limits:
 - a) Bone, cartilage, osteoarticular grafts, tendons, meniscus, and fascia lata:
 - i. history of osteo-arthritis,
 - ii. metabolic bone diseases (osteoporosis, osteopetrosis, Paget's disease, etc...),
 - iii. suicide by ingesting cyanide or heavy metals (mercury, gold, etc..),
 - b) Cartilage and osteoarticular grafts additionally:
 - i. iatrogenic or degenerative lesions detected during retrieval
 - c) Meniscus additionally:
 - i. iatrogenic or degenerative meniscus tears detected during retrieval
 - d) Tendons additionally:
 - i. iatrogenic or degenerative tendon tears detected during retrieval
2. Musculoskeletal tissue retrieval from deceased donors should occur as soon as possible after death, however no later than forty eight (48) hours post mortem if 12 hours after death body was cooled otherwise retrieval should occur no later than 24 hours after death. All time intervals for each donor (death to enucleation and preservation) should be recorded.

F.1.3.3.2.4.1.3. Infections

Persons with significant local bacterial, viral, parasitic or mycotic infection including cannot be considered as musculoskeletal tissue donors.

F.1.3.3.2.4.1.4. Invalid laboratory test results

Tissue banks may only accept tissue from donors with a plasma dilution of more than fifty (50) per cent, if the test methods applied to such plasma are validated.

F.1.3.3.2.4.1.5. Vaccination

Persons who received a post expositional vaccination against rabies within the last twelve (12) months or a live vaccination, e.g. against poliomyelitis, yellow fever, rubella, measles, mumps, within the last four (4) weeks prior to removal of the cornea cannot be considered as donors.

F.1.3.3.2.4.1.6. Donor age

Donor age limit differs in different kind of musculoskeletal tissues. Age limits are as follows:

- a) for bone minimum age: 15 years for both sexes;
- b) for tendons and fascia lata: 15-65 years for both sexes;
- c) for osteo-articular, cartilage, meniscus: 15-45 years for both sexes;
- d) for chondrocytes culture : 15-55 years for both sexes.

F.2. RECOVERY

F.2.1. ACTIVITIES

F.2.1.1. Access to the operating room or other recovery room

See generic requirements in section A.4.1.1.

F.2.1.1.1. General

See generic requirements in section A.4.1.3.1.

F.2.1.1.2. Deceased donors

The entire retrieval of the musculoskeletal donor is to be performed like during autopsy. Tissue recovery is to be performed using validated aseptic procedures.

F.2.1.1.2.1. Donor identification

Prior to tissue recovery, the donor should be positively identified by cross-check with a tag or other label on the body, or by positive identification by hospital or mortuary staff.

F.2.1.1.2.2. Gowning

Staff performing the retrieval is to be dressed appropriately for the kind of retrieval to minimize the risk of contamination of the tissue to be removed and also the hazard for the performing staff. This includes due disinfection (surgical hand disinfection), sterile clothes as well as to wear sterile gloves, face mask or protective mask and surgery cap.

F.2.1.1.2.3. Donor preparation

The donor skin should be cleaned using a suitable disinfectant (e.g. PVD iodine), a local sterile area should be created in the area of retrieval using sterile cloths.

F.2.1.1.2.4. Procurement of long bones of the lower limb

A skin incision begun from the anterior superior iliac process extending over the greater trochanter, distally along the lateral thigh towards the anterior knee over the patellar tendon and extended distally over the anterior tibial crest up to the ankle.

F.2.1.1.2.4.1. Procurement of the femur

Fascia lata must be incised, surrounding muscles are to be dissected and femur must be disarticulated at the knee level. In the next stage the hip abductors must be released and the thigh muscles elevated. The femur than, must be internally rotated and the hip capsule incised close to the acetabulum. The femur may be removed.

F.2.1.1.2.4.2. Procurement of the tibia and the fibula

Muscles must be elevated laterally and medially. The inter-osseous membrane must be incised close to the tibia. The proximal and distal tibio-fibular joints must be disarticulated. The tibia and fibula may be removed.

F.2.1.1.2.5. Procurement of the iliac crest or hemipelvis

To recover the iliac crest, the incision described in F.2.3.2.2.4. must be extended from the anterior superior iliac process posteriorly. Soft tissues must be removed and after the sacroiliac joint and the symphysis pubis disarticulation the piece of iliac crest or hemipelvis may be removed. If bowel perforation occurs, harvesting of the pelvis should be terminated.

F.2.1.1.2.6. Procurement of long bones of the upper limb

A skin incision begun at the coracoid process, extending along the deltopectoral groove, then extending along the anterolateral aspect of the arm to the elbow, then distally along the radial aspect of the forearm.

F.2.1.1.2.6.1. Procurement of the humerus

The rotator cuff must be transected at musculotendinous junction, leaving the tendinous portion attached to the proximal humerus. The humerus must be disarticulated at the arm and elbow levels. The humerus may be removed.

F.2.1.1.2.7. Procurement of the rib

Incisions must be made directly over the ribs extending from the costal margins to the posterior vertebral attachment. Surrounding intervertebral muscles must be dissected, disarticulation at the costo-vertebral joint and the sternum must be made. The rib may be removed.

F.2.1.1.2.8. Procurement of the fascia lata

Fascia lata is excised before removal of the femur as described in F.2.3.2.2.4.1.

F.2.1.1.2.9. Procurement of Achilles tendon

The Achilles tendon may be recovered during procurement of the tibia and the fibula (see F.2.1.2.2.4.2.) together with an attached bone block from the calcaneus.

F.2.1.1.2.10. Procurement of the patellar tendon

The patellar tendon should be removed with a block of tibial tubercle distally and the patella proximally using the anterior incision over the knee joint and quadriceps muscles. The soft tissues must be cleared approximately 12 cm above and below the joint line. The femur and tibia-fibula must be osteotomised. Patellar tendon may be procured during or during procurement of long bones of the lower limb (F.2.1.2.2.4.).

F.2.1.1.2.10. Procurement of the menisci

The menisci are usually left attached to the tibia and can be procured after tibia removal from the donor.

F.2.1.1.2.11. Reconstruction of the donor's body after procurement

A wooden stick or a plastic bone approximating the size of the donor bone may be used to replace the procured bone. The split muscles should be resutured using surgical sutures followed by subcutaneous tissue and skin. The natural anatomic contours of the body must be restored.

F.2.1.2.3. Living donors

Musculoskeletal tissues can be procured from living donors.

F.2.1.2.3.1. Living allogenic donors

F.2.1.2.3.1.1 Femoral head donors

Patients subjected to surgical procedure of hip replacement can be considered as living donors of femoral heads. Removed bone fragment that is replaced by prosthesis can be donated.

F.2.1.2.3.2. Living autogenic donors

F.2.1.2.3.2.1. Cranial flap

Cranial flaps removed during neurosurgical procedures can be donated for autologous grafting when it is impossible to place the craniotomy flap due to the brain oedema.

F.2.1.2.3.2.2. Cartilage for chondrocyte culture

Cartilage fragment from the unloaded part of the knee joint cartilage may be procured during surgical procedure (e.g. knee arthroscopy)

F.2.1.3. Processing during recovery

See generic requirements in section A.4.1.4.

F.2.1.4. Quality control

See generic requirements in section A.5.1.4.

F.2.1.5. Packaging and labelling

See generic requirements in section A.4.1.5.

F.2.1.5.1. Primary packaging and labelling

Subsequently to retrieval the obtained musculoskeletal tissues are to be packaged in a way to minimize the contamination risk. Each procured tissue is to be packed separately and labelled immediately after recovery

F.2.1.5.1.1 Packaging for hypothermic storage

Musculoskeletal tissues are to be at least double packed in air tight foil packages.

F.2.1.5.1.2. Packaging for cell culture

For packaging of cartilage biopsy tissue banks should use a sterile, sealable container containing appropriate normothermic chondrocyte transport medium in accordance with manufacturer's recommendations. An established medium for that purpose might be PBS (phosphate buffer saline) and DMEM-F12 culture medium with or without FBS (foetal bovine serum).

F.2.1.6. Storage and transport after recovery

See generic requirements in section A.4.1.6.

F.2.1.6.1. Storage after tissue recovery

F.2.1.6.1.1. Storage temperatures

The procured musculoskeletal tissues are to be stored at temperatures appropriate to maintain their characteristics and biological functions suitable for the intended use. These temperatures principally correspond to the storage temperatures specified below in dependence of the method.

- The musculoskeletal donor tissues should be stored at hypothermic conditions. Storage temperatures according to validated protocol should be 2-8°C or in temperatures from -30 to -70°C (on dry ice, in freezers or deep-freezers). It is also accepted to store musculoskeletal tissues in liquid nitrogen containers at temperatures between -75°C to -196°C.
- The cartilage for chondrocyte culture should be stored at 4 to 8 °C in the refrigerator.

F.2.1.6.1.2. Storage time

F.2.1.6.1.2.1. Storage time for hypothermic storage

A storage period should be evaluated and validated. Usual storage period do not exceed 3 months after procurement.

F.2.1.6.1.2.2. Storage time for cell culture

A storage period should be evaluated and validated. Usual storage period do not exceed 3 days.

F.2.1.6.2. Transport after tissue recovery

Musculoskeletal donor tissues are to be transported at appropriate temperatures to maintain their characteristics and biological functions. Principally these temperatures correspond to the storage temperatures (see chapter F.2.3.6.1.), depending on the tissue and the method of cultivation.

The package and the mode of transport are to be chosen in a way to ensure maintenance of the tissue specific storage temperatures (see chapter B.2.3.6.1). This is to be monitored by the tissue bank in regular intervals. If temperature stability should not be reliably guaranteed by the pack or mode of transport used also in cases of unexpectedly high or low

environmental temperatures, a temperature recording unit is to be enclosed that is to measure the temperature inside the pack in minimally half-hour intervals and save the data. In addition, the pack is to prevent contamination by persons in charge of tissue packaging and transport.

The transport time of donor cartilage for chondrocytes culture should be kept as short as possible.

F.2.1.7. Documentation and release for processing

See generic requirements in section A.4.1.7.

F.3. PROCESSING

F.3.1. ACTIVITIES

F.3.1.1. Reception

See generic requirements in section A.5.1.5.

F.3.1.2. Access to the processing facilities

See generic requirements in section A.5.1.2.

F.3.1.3. Processing

F.3.1.3.1. General

See generic requirements in section A.5.1.3

F.3.1.3.2. Processing methods

Proof is required that the validated procedures are performed by the tissue bank staff in a uniform manner in accordance with the approved standard operating procedures.

F.3.1.3.2.1. Processing of tissues and cells

See generic requirements in section A.3.3.3.2.1

There are various methods used for bone processing by individual tissue banks. From cadaveric donors cancellous and cortico-cancellous, cortical, osteochondral, ligaments and tendons allografts can be processed. Living donor allogeneic and autologous bone allografts are processed in the same manner as allografts. In-between the working steps the bone tissue should be stored at a short time at -40°C, better at -80 °C or kept on ice.

Living donor autogenic chondrocyte culture requires in vitro cell culture procedures.

F.3.1.3.2.1.1. Cancellous and cortico-cancellous bone processing

Cancellous and cortico-cancellous bone grafts might be prepared from epiphysis of distal femur and proximal tibia, proximal and distal epiphysis of humerus and vertebral bodies and iliac crest. Bone tissue should be clinched from the remaining soft tissues mechanically. Long bones should be cutted in the border between diaphysis and epiphysis (metaphysis) using different kind of saws (e.g. banding saw, oscillating saw). Final shape of the graft is then achieved.

F.3.1.3.2.1.2. Cortical bone processing

Cortical bone grafts might be prepared from diaphysis of procured long bones: the femur, tibia, fibula, humerus, radius and ulna. Bone tissue should be clinched from the remaining soft tissues mechanically. Shape of the graft can be achieved by different kind of saws (see F.3.1.3.2.1.2.)

F.3.1.3.2.1.3. Osteochondral bone processing

Osteochondral bone grafts might be prepared from distal or proximal femur, tibia humerus, radius and ulna. Bone tissue should be clinched from the remaining soft tissues mechanically. The shape of the final graft can be achieved by different kind of saws (see F.3.1.3.2.1.2.)

F.3.1.3.2.1.4. Ligaments and tendons processing

Achilles and patellar tendons as well as ligaments should be cleaned mechanically.

F.3.1.3.2.1.5. Washing and defatting procedure

Washing and defatting procedure is used to remove cells from cancellous and cortical bone tissue. In the mechanical cleaning process the entire bone marrow is to be removed. Two different methods may be applied: chloroform/methanol (or ethanol) solution (shares of volume 2 : 1) or warm water or saline solutions. In-between the steps of that procedure the rinsing solution should be exchanged. An optical control of the bone as regards structural integrity should be made.

F.3.1.3.2.1.5.1. Defatting procedure

Chloroform/methanol or chloroform/ethanol mixture or alcohol alone should cover the bone to be defatted. The procedure should be done using shaking machine for a period of approximately two hours. In the next step the bone will be rinsed four times in methanol (or

ethanol) to remove the chloroform effectively. Finally a rinsing with water or saline solution should be made.

F.3.1.3.2.1.5.2. Washing procedure

Alternatively the removal of cells might be done with a sharp jet or shaking machine with water or saline solution. Warm water in temperature 30°C might be used.

F.3.1.3.2.1.6. Lyophilisation

The moisture is extracted from the bone by a process of freezing and prevention of ice formation. The purpose is to permit shelf storage at room temperature. The moisture content at the end of freeze-drying should be less than 5%

F.3.1.3.2.1.7. Demineralisation

Grounded bone (standardized diameter: 80-300 micron, 300-425 micron, 425-600 micron, 600-1000 micron) by freezer mill is subsequently demineralised in acid solution for 90 minutes (e.g. 0.5 or 0.6 M HCl). In next step bone is defatted (as described in F. 3.1.3.2.1.5.1.) and alternatively lyophilised (as described in F. 3.1.3.2.1.6.) or freezed. The amount of calcium (usually less than 10%) content should be calculated (e.g. percent of calcium of bone matrix dry weight).

F.3.1.3.2.1.8. Autologous chondrocyte culture

Samples of articular cartilage should be submitted to enzyme digestion process to isolate cells. After isolation, cells are cultured in the incubator at standard conditions (temperature - 37°C, CO₂ – 5%, humidity - 95%) in culture flasks with medium (e.g. HAMF12 or DMEM, penicillin/streptomycin 1% and fetal bovine serum 10%) for period of 4-6 weeks. The medium should be changed twice or three times per week. Total cells and percentage of viable cells should be counted after cell isolation and at the end of cultures (e.g. trypan blue in a hemocytometric chamber or in a cell counter). There should be calculated number of viable cell and the average number of cells (cell density). Morphological analyses of cells should be routinely performed using microscope. After enzymatic digestion cultured chondrocytes might be transferred into three dimensional scaffolds (e.g. fibrin glue, aginate rings).

F.3.1.3.2.2. Sterilisation or decontamination of musculoskeletal tissues and cells

For sterilisation and decontamination wide range of procedures can be used. Sterilisation procedure should assure that none of the viable organisms will be present in the sample after sterilisation. The term Sterility Assurance Level was introduced as the expected probability of a surviving micro-organism on an individual product unit after exposure to a valid sterilisation process. SAL 10^{-6} was established for product with direct contact to human tissues and means, that there is probability of survival of 1 microorganism of 1 mln present in the product.

F.3.1.3.2.2.1. Sterilisation

1. Radiation sterilisation; Both gamma rays and accelerated electron beam might be used for sterilisation process. The technique (irradiation dose, temperature of irradiation) must be validated, considering the initial contamination (bioburden) and other factors influencing effectiveness if radiation-sterilisation (e.g. presence of oxygen, physical state of irradiated graft). No specific dose can therefore be recommended. Doses used for sterilisation ranged from 17 to 35 kGy and are established after calculation of initial contamination. The irradiation process must be always documented.
2. Ethylene oxide sterilisation; the graft should be exposed to the quantity of ethylene oxide recommended by the manufacturer. It should be guaranteed that the procedure meets the requirements of temperature, humidity and gas concentration. After a treatment with ethylene oxide, a ventilation process need to be followed, allowing the elimination of residual ethylene oxide and its by-products (e.g. ethylene chlorohydrins and ethylene glycol). For each batch of ethylene oxide, chemicals indicators should be used. It should be demonstrated that sterilization was reached for each batch of tissue. Representative samples of each batch must be tested to detect the presence of oxide residual ethylene or decomposition products due to the toxicity of chemical residues. The tissue treated with ethylene oxide must then be frozen at a minimum of -40 ° C, or be lyophilized and stored at room temperature.

F.3.1.3.2.2.2 Decontamination

1. Chemical decontamination; there are many chemicals having a decontamination function or an inactivating effect on specific pathogens (e.g. paracetic acid, iodophors, ethanol). The effectiveness of these agents on certain types of tissue must be validated. It is important to mention the chemicals used in the documentation accompanying the graft.

It is also necessary to mention the nature of these chemicals products and the possible presence of traces of these products or decomposition products.

2. Antibiotic decontamination; for decontamination of musculoskeletal tissue antibiotics may be used. The effectiveness of each antibiotic cocktail should be validated and documented. The use of antibiotic decontamination procedure might be the only method microbial inactivation for chondrocyte cell culture.

F.3.1.4. Quality control

The quality control tests on musculoskeletal grafts should consider at least the following minimum quality criteria:

- a) Morphology and integrity of the musculoskeletal grafts
- b) Shape and a size of a graft
- c) Moisture residue in lyophilised grafts
- d) Calcium content in demineralised bone
- e) Sterilisation indicators
- f) Number of viable cells and cell density in chondrocyte culture
- g) No evidence of microbiological growth or malignant cells

See generic requirements in section A.5.1.4.

F.3.1.4.1. Microbiological control

F.3.1.4.1.1. General Principle

See generic requirements in section A.5.1.4.1

Additionally, antimicrobial effects of antibiotics in the culture medium solution should be taken into account while choosing and validating the microbiological test method for chondrocyte culture.

F.3.1.4.1.2. Methods

F.3.3.4.1.2.1. Microbiological controls for musculoskeletal tissues

During procurement microbiological samples should be collected to establish initial contamination of tissues to make a decision during quarantine regarding release of procured material for further processing. Those microbiological tests are also important to control

procurement procedure. There might be two techniques of sampling for microbiological testing:

- swabs – collection of potential microorganisms from the surface of tissues
- destructive method – a biopsy taken from procured tissues.

During processing microbiological samples should be collected before packaging of a final product. There might be three techniques of sampling for microbiological testing:

- swabs
- destructive method
- collection of the last portion of the fluid used for washing of tissue graft.

F.3.3.4.1.2.2. Microbiological controls for cultured chondrocytes

During processing in cell culture at least two microbiological tests should be performed. First sampling of the transport medium should be performed parallel to the enzyme digestion process of articular cartilage.

The second microbiological test should be performed in the end of a chondrocyte culture before release for the clinical use.

In the mean time the culture medium should be regularly inspected for cloudiness, which may indicate contamination. If visible cloudiness or decolouration of the culture medium should occur, suitable microbiological testing should be initiated.

F.3.1.5. Packaging and labelling

See generic requirements in section A.5.1.5.

F.3.1.6. Storage/ preservation

F.3.1.6.1. General

See generic requirements in section A.6

Additionally, it must be recognized that while maximum storage times are recommended for the various methods of tissue preservation, in most cases it is preferable to transplant tissues before these maximum times are approached in order to optimize surgical outcome. Availability of tissue, clinical requirements and surgical need may determine the storage time for each individual tissue.

F.3.1.6.2. Methods of preservation and storage

Preservation/storage methods for recovered donor musculoskeletal tissue are presented in chapter F.2.3.6.

F.3.1.6.2.1. Preservation and storage in hypotermic conditions

1. The packaging material should be validated for storage in hypotermic conditions. The integrity of packaging material plays an important role for assuring microbiological safety.

2. Preservation and storage in the freezer

Preservation and storage of musculoskeletal tissues in the freezer at -20°C to -30°C should not exceed 6 months. Using this method, cancellous, cortico-cancellous, cortical, ligaments and tendons allografts can be preserved and stored.

3. Preservation and storage in deep freezer

Preservation and storage of musculoskeletal tissues in the deep-freezer at -60°C to -80°C allows prolong the storage time up to 5 years. Using this method cancellous, cortico-cancellous, cortical, ligaments and tendons allografts can be preserved and stored.

4. Cryopreservation and storage

Cryopreservation is a process where tissues are preserved by cooling to temperatures approx. -196 °C (the boiling point of liquid nitrogen). Process starts with controlled cooling to -80°C. Using this method cancellous, cortico-cancellous, cortical, ligaments and tendons allografts can be preserved and stored. This method is suitable for osteochondral and cells preservation and storage. Cryoprotectants (e.g. glycerol, DMSO - dimethyl sulfoxide) to avoid ice crystal formation that destroy cells are added to freezing medium. The storage time in these conditions should not exceed 5 years.

5. Preservation and storage at room temperature

All kinds of lyophilised musculoskeletal allografts might be stored at room temperature. There is no time limit for storage of lyophilised grafts. The only limitation is the integrity of packaging material to assure microbiological safety and reduced moisture.

6. Tissue culture of chondrocytes

Cultured chondrocytes in conditions described in F.3.1.3.2.1.8. might be cryopreserved with presence of cryoprotectant as described in F.3.1.6.2.1.3. and stored at -196°C. Cultured chondrocytes might be transported in frozen state.

Alternatively, cultured chondrocytes (F.3.1.3.2.1.8) prior to transplantation should be transferred into transport medium. During transport temperatures should range between 2°C to 8°C.

F.3.1.6.3. Storage area

See generic requirements in section A.6

F.3.1.7. Documentation and release

F.3.1.7.1. General

See generic requirements in section A.5.1.6.1.

F.3.1.7.2. Release

Before tissues are released for transplantation, all tissue bank records concerning donor screening, testing and quality control should be reviewed and found to be complete and accurate. Final release for transplantation is to be performed and signed by the responsible person. The documentation for the release of donor tissue is to demonstrate that all specifications were met, especially that all effective notification forms, medical records, processing, sterilisation and storage records were inspected.

F.3.1.7.2.1. Release of musculoskeletal tissue grafts

The tissue bank should establish and document their criteria for release of tissue for transplantation, which should include (but is not limited to), the following:

- a) Full donor screening for contraindications with normal result.
- b) Negative serological or molecular biological diagnosis of the donor.
- c) Acceptable microbiological test results.
- d) Comparison of recipient's for autologous use
- e) Macroscopic morphology and integrity of a graft.
- f) Shape and size of the graft compared with final label.
- g) Sterilisation/decontamination protocol and indicator of process if exists.
- h) Moisture residue (water content) in lyophilised grafts.
- i) Calcium content in demineralised bone.

j) Integrity of packaging material.

F.3.1.7.3. Processing file contents

See generic requirements in section A.5.1.6.3.

F.3.1.7.4. Availability for inspection

See generic requirements in section A.5.1.6.4.

F.3.1.7.5. Traceability

See generic requirements in section A.5.1.6.5.

SECTION G

G.1. GLOSSARY

ALLOGENEIC USE: cells or tissues removed from one person and applied to another.

AUTOLOGOUS USE: cells or tissues removed from and applied to the same person.

BANK OF TISSUES AND CELLS: unit which meets the requirements of national laws and regulations to carry out activities of production, testing, processing, storage and distributing of tissues and/or cells, including import and export, and that is approved for that purpose by the Federal Public Service Public Health.

BIOBURDEN: The level and type (e.g. objectionable or not) of micro-organisms that can be present in raw materials, or advanced therapy medicinal products. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

CALIBRATION: The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.

CELLS: individual human cells or a collection of human cells when not bound by any form of connective tissue.

CLEAN AREA: An area with defined environmental control of particulate and microbial contamination constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area. (Note: The different degrees of environmental control are defined in the Supplementary Guidelines for the Manufacture of sterile medicinal products)

CONTAMINATION: The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material or advanced therapy medicinal product during processing, sampling, packaging or repackaging, storage or transport.

CONTROLLED AREA: An area constructed and operated in such a manner that some attempt is made to control the introduction of potential contamination (an air supply approximating to grade D may be appropriate), and the consequences of accidental release of living organisms. The level of control exercised should reflect the nature of the organism employed in the process. At a minimum, the area should be maintained at a pressure negative to the immediate external environment and allow for the efficient removal of small quantities of airborne contaminants.

CRITICAL: potentially having an effect on the quality and/or safety of or having contact with the cells and tissues.

CROSS CONTAMINATION: Contamination of a material or of a product with another material or product.

DEVIATION: Departure from an approved instruction or established standard.

DISTRIBUTION: transportation and delivery of tissues or cells for human applications.

DIRECTED DONATION: The donation to a specific recipient.

DONOR: every human source, whether living or deceased, of human cells or tissues.

DONATION: donating human tissues or cells intended for human applications.

EXPIRY DATE (OR EXPIRATION DATE): The date placed on the container/labels of an advanced therapy medicinal product designating the time during which this product is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.

FINISHED PRODUCT: The product which has undergone all stages of production, including packaging in its final container.

HUMAN APPLICATION: the use of tissues or cells on or in a human recipient and extracorporeal applications.

INFECTED: Contaminated with extraneous biological agents and therefore capable of spreading infection.

INFORMED CONSENT: Written permission for donation of tissues and cells and for the ulterior use of them. The donor, one of his relatives or his legal representative must have understood the nature of the donation and the proposed use and accept any implied risks before giving legal consent.

IN-PROCESS CONTROL: Checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms its specification. The control of the environment or equipment may also be regarded as a part of in-process control.

ORGAN CULTURE: a method for medium-term conservation of tissues in medium of cellular culture (particularly applicable to corneas)

ORGANISATIONS RESPONSIBLE FOR HUMAN APPLICATION (ORHA): a health care establishment or a unit of a hospital or another body which carries out human application of human tissues and cells.

PACKAGING MATERIAL: Any material employed in the packaging of the grafts excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

PARTNER DONATION: The donation of reproductive cells between a man and a woman who declare that they have an intimate physical relationship.

PRESERVATION: The use of chemical agents, alterations in environmental conditions or other means during processing to prevent or retard biological or physical deterioration of cells or tissues.

PROCESSING: all operations involved in the preparation, manipulation, preservation and packaging of tissues or cells intended for human applications.

PROCUREMENT ORGANISATION: a health care establishment or a unit of a hospital or another body that undertakes the procurement of human tissues and cells and that may not be accredited, designated, authorised or licensed as a tissue Establishment.

QUALIFICATION: Action of proving that any equipment works correctly and actually leads to the expected results. The word validation is sometimes widened to incorporate the concept of qualification.

QUALITY ASSURANCE: The sum total of the organised arrangements made with the object of ensuring that the product is of the quality required for its intended use and that quality systems are maintained.

QUALITY CONTROL: Checking or testing that specifications are met.

QUALITY MANAGEMENT: the coordinated activities to direct and control an organisation with regard to quality.

QUALITY SYSTEM: the organisational structure, defined responsibilities, procedures, processes, and resources for implementing quality management and includes all activities which contribute to quality, directly or indirectly.

QUARANTINE: the status of retrieved tissue or cells, or tissue isolated physically or by other effective means, whilst awaiting a decision on their acceptance or rejection.

RECIPIENT: the human person on or in which tissues or cells are used.

RECONCILIATION: A comparison, making due allowance for normal variation, between the amount of product or materials theoretically and actually produced or used.

RELEASE: the provision of tissues or cells by a tissue bank for transplantation/ implantation to a recipient

RETURN: Sending back to the tissue establishment of a product which may or may not present a quality defect.

SERIOUS ADVERSE EVENT: any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a

communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity.

SERIOUS ADVERSE REACTION: an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity.

TISSUE ESTABLISHMENT DOSSIER: document which contains general and specific information concerning the activities and procedures of the organisation concerned.

SPECIFICATION: A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. ‘Conformance to specification’ means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

STANDARD OPERATING PROCEDURE (SOP): written instruction describing the steps in a specific process, including the materials and methods to be used and the expected end product.

STERILITY: Sterility is the absence of living organisms. The conditions of the sterility test are given in the European Pharmacopoeia.

STORAGE: maintaining the product under appropriate controlled conditions until distribution.

TISSUE: all constituent parts of the human body formed by cells.

TISSUE ESTABLISHMENT: a tissue bank or a unit of a hospital or another body where activities of processing, preservation, storage or distribution of human tissues and cells are undertaken. It may also be responsible for procurement or testing of tissues and cells.

TRACEABILITY: the ability to locate and identify the tissue/cell during any step from procurement, through processing, testing and storage, to distribution to the recipient or disposal, which also implies the ability to identify the donor and the tissue establishment or the manufacturing facility receiving, processing or storage the tissue/cells, and the ability to identify the recipient(s) at the medical facility/facilities applying the tissue/cells to the recipient(s); traceability also covers the ability to locate and identify all relevant data relating to products and materials coming into contact with those tissues/cells.

TRANSFORMATION: any activity related to the preparation, handling, storage and packaging of tissues or cells for human applications.

VALIDATION (OR ‘QUALIFICATION’ IN THE CASE OF EQUIPMENT OR ENVIRONMENTS): means establishing documented evidence that provides a high degree of

assurance that a specific process, piece of equipment or environment will consistently produce a product meeting its predetermined specifications and quality attributes; a process is validated to evaluate the performance of a system with regard to its effectiveness based on intended use.

G.2. ACRONYMS

ATMP	Advance Therapy Medicinal Products
CA	Competent authority
CoE	Council of Europe
DALK	Deep Anterior Lamellar Keratoplasty
DLEK	Deep Lamellar Endothelial Keratoplasty
DSAEK	Descemet's Stripping Automated Endothelial Keratoplasty
DQ	Design qualification
EBMT	European Group of Blood and Marrow Transplantation
EQSTB	European Quality System for Tissue Banking
EU	European Union
EUTCD	European Union tissue and cells directives
FBS	Foetal bovine serum
GMP	Good Manufacturing Practices
GTP	Good tissue practice
HLA	human leukocyte antigen
HVAC	heating, ventilation, and air conditioning
ICH	International Conference on Harmonisation
ICT	Information and Communication Technologies
ID	Identification
IPC	In process control
IQ	Installation qualification
JACIE	The Joint Accreditation Committee-ISCT
LASIK	Laser in situ keratomileusis
LKP	Lamellar Keratoplasty
MEM	Minimum Essential Medium
OQ	Operational qualification
OR	Operating room
ORHA	Organization responsible for human application
PKP	Penetrating Keratoplasty
PQ	Performance qualification
PRK	Photorefractive keratectomy
PTK	Photo-Therapeutic Keratectomy
QA	Quality assurance
QC	Quality control
RP	Responsible person
SAE	Serious adverse event
SAR	Serious adverse reaction
SOP	Standard operating procedures

TE	Tissue establishment
vCJD	Variant Creutzfeldt-Jakob disease
WHO	World Health Organization

G.3. REGULATION OF REFERENCE

G.3.1. EUROPEAN UNION

1. Directive **2004/23/EC** of the European Parliament and the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation and storage of tissues and of cells. Official Journal of the European Union. L102, 7.4.2004. p.48.
2. Commission Directive **2006/17/EC** of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and the Council of 31 March 2004 concerning certain technical requirements for donation, procurement and control tissues and cells of human origin. Official Journal of the European Union. L38, 9.2.2006. p.40.
3. Commission Directive **2006/86/EC** implementing Directive 2004/23/EC of the European Parliament and the Council of 31 March 2004 concerning certain technical requirements for processing, preservation and storage of tissues and cells. Official Journal of the European Union. L294, 25.10.2006. p.32.

G.3.2. COUNCIL OF EUROPE

1. Resolution (78) 29 on the harmonization of legislations of member states relating to removal, grafting and transplantation of human substances.1978
2. Recommendation (94) 1 of the committee of Ministers to Member States on Human Tissue Banks.1994
3. Recommendation (94) 1 on human tissue banks.1994
4. Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine.1997
5. Standardisation of organ donor screening to prevent transmission of neoplastic diseases. 1997
6. State of the art report on serological screening methods for the most relevant microbiological diseases of organ and tissue donors.1997

7. Recommendation (98) 2 on provision of hematopoietic progenitor cells.1998
8. Recommendation Rec (2001)4 of the Committee of Ministers to member states for the prevention of the possible transmission of variant Creutzfeldt-Jakob disease (vCJD) by blood transfusion.2001
9. Additional protocol to the Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine, on transplantation of organs and tissues of human origin, 2002.

G.3.3. WORLD HEALTH ORGANIZATION

1. Report of the First Global Consultation on Safety and Quality Requirements for Cells and Tissues for Transplantation, Ottawa, November 2004.
2. Report of the Second Global Consultation on Safety and Quality Requirements for Cells and Tissues for Transplantation, Geneva, 7-9 June 2006
3. Aide-Mémoire on Key Safety Requirements for Essential Minimally Processed Human Cells and Tissues for Transplantation
4. Aide-Mémoire on Access to Safe and Effective Cells and Tissues for Transplantation
5. Guiding Principles on Human Cell, Tissue and Organ Transplantation as endorsed by the sixty-third World Health Assembly in May 2010, in Resolution WHA63.22

G.3.4. REFERENCE STANDARDS

1. General Standards for Tissue Banking, European Association of Tissue Banks.
2. Standards for Tissue Banking. American Association of Tissue Banks
3. Common Standards for Musculo-skeletal Tissue Banking. European Association for Tissue Banks & Association of Musculo-Skeletal Transplantation.
4. Standards for blood and marrow progenitor cell processing, Ishag & EMBT.
5. Technical Guidelines for Ocular Tissue, European Eye Bank Association.
6. Medical Standards, European Eye Bank Association.
7. Medical Standards, Eye Bank Association of America.
8. Medical and Quality Standards for Eye Donation and Eye Tissue Banking, Eye Bank Association of Australia and New Zealand Inc.

9. European Good Manufacturing Practices

10. JACIE standard is the EBMT website: <http://www.embt.org/transplantGuidelines>

11. The rules governing Medicinal products in the European Union on the website:
<http://pharmacos.eudra.org/f2/eudralex/index.htm>

G.4. TISSUE ESTABLISHMENT DOSSIER

1. The aim of this document is to provide general and specific information of TE or ORHAs and TEs concerning their activities. This information can be useful for themselves and for the competent authorities during inspection preparation.
2. The Tissue Establishment Dossier should be based in the following document, containing at least the information required on it, although other information could be added.

See Annex I (EUSTITE Tissue Establishment Dossier)

G.5. EQSTB CHECKLIST

See Annex II (GUIDE FOR AUDITING TISSUE ESTABLISHMENTS)

Annex I

EUSTITE Tissue Establishment Dossier

Annex 6 – Proposed Common Format for a ‘Tissue Establishment Dossier’

Tissue Establishment Dossier (TED)

Please complete one dossier for each site if the TE has more than one site

Section A – General Information

Full Name of TE

TE Mailing Address

Telephone Number

Fax Number

Email address:

Activity Summary: Please tick the relevant boxes to indicate the activities carried out on site:

PRESCRIBED ACTIVITY: Donation Procurement Testing Processing Storage Distribution Import Export	TISSUES: Skeletal Skin Vascular Corneas Amniotic Membrane Other	PROCESSES (including contracted processes): Cutting/grinding/shaping Soaking in antibiotic or antimicrobial solutions Sterilisation (not by irradiation) Irradiation Cell separation, concentration, purification Filtering Lyophilisation (Freeze-drying) Freezing Cryopreservation Vitrification Drying Deminerallisation Storage in Organ culture medium 4°C storage Glycerolisation (high concentration) Volume reduction Centrifugation Sperm preparation (including washing and centrifugation) IVF without ICSI IVF with ICSI Other
Reference number/code of the Competent Authority processing authorisation (if available)		

Section B – Activity - Details

Please attach a flow-chart which describes the full activity of the TE

Does the TE conduct procurement?

YES/NO

(If no, indicate which procurement organisations provide tissues/cells to the TE)

Does the TE conduct donor testing?

YES/NO

(If no, indicate which organisation(s) conducts testing of the tissue/cell donors)

Types of tissues/cells received by the TE (from own procurements or procurements by others)
(please list here or attach separately)

Number of donors from whom tissue/cells were received at the TE in the previous year

Living allogeneic (unrelated, non-partner):

Living allogeneic (related or partner):

Living autologous:

Deceased:

Types of tissues/cells processed by the TE
(please list here or attach separately)

How have the processing methods applied been validated to demonstrate that they do not render the tissue clinically ineffective or toxic for the recipient?
 (not necessary to complete if Preparation Process Dossier is used)

- a) by studies conducted at your TE?
- b) by published studies?
- c) by retrospective analysis of clinical results?
- d) other (please specify):

In-process and final Quality Control testing methods applied to the tissues or cells

(please list here or attach separately)

Types of finished tissues/cells distributed by the TE
 (please list here or attach separately)

.....

Does the TE receive finished tissues/cells from other TEs in the same EU Member State for distribution?

YES/NO
 (if yes, indicate which type of tissue and provide the name(s) of the TE(s))

Does the TE receive tissues/cells from other TEs in another EU member state for distribution?

YES/NO
 (if yes, indicate which type of tissue/cells and name(s) the country(ies) of origin and the name(s) of TE(s))

Does the TE import tissues/cells from outside the EU for distribution?

YES/NO
 (if yes, indicate which type of tissue/cells and name(s) the country(ies) of origin and the name(s) of TE(s))

Number of tissue or cell units (individual packages, bags, straws or vials) distributed by the TE for human application in the previous year

.....

Section C – Personnel

Name of Responsible Person as defined in Directive 2004/23/EC
(Please attach a brief curriculum vitae)

Name of TE Director
(if different from above)
(Please attach a brief curriculum vitae)

Name of Medical Director
(if different from above)
(Please attach a brief curriculum vitae)

Name of Quality System Manager
(Please attach a brief curriculum vitae)

Name of Processing Manager (where relevant)
(Please attach a brief curriculum vitae)

Total number of staff

**Provide a functional organisational chart which identifies roles and reporting relationships
(Insert in the space provided or attach separately).**

Please indicate in the organisational chart how many people are working in donor selection, procurement, processing, quality control, quality assurance, administration, storage and transport)

Section D – Facilities

Please describe the processing and storage facilities. Please indicate the number of rooms, their dimensions and environmental classification, where relevant.

(Please attach a plan of the area, the rooms (numbered), their dedication as well as personnel, tissue or cells, personnel, material and waste flow)



Section E – Equipment

Please provide a list of the critical equipment used for processing and testing.



Please describe the system used to support traceability (if relevant)



Section F – Contracts/Agreements with other Organisations

Are any prescribed activities carried out by a third party (from procurement to distribution)?

YES/NO

(If yes, indicate which steps and name the organisation that acts as the third party). Please provide copies of relevant agreements

Section G – Transportation

Please describe the arrangements in place for the transport of each type of tissues or cells from procurement to the TE

Please describe the arrangements in place for the transport of each type of tissue or cells from the TE to the Organisation Responsible for Human Application

Section H – Adverse Event and Reaction Reporting

Please describe the arrangements in place for the reporting and management of SAE and SAR

Section I – Quality System

Please give a brief description of the quality system applied at the TE.
Please attach a list of the SOPs in place

Has the TE been certified by any external body or professional society	YES/NO (If yes, please give details of when and by whom and add certification number)
---	---

Section J – Signature and Date

Signature of Responsible Person

Date:

Section K – Instructions for the Submission of this Form

This form should be submitted as an initial application for accreditation/designation/authorisation/licensing by the Competent Authority for tissues and cells. It should be re-submitted when significant changes in activity, staffing or processes applied have taken place or when there are significant changes to any of the attached documents.

Changes considered to be significant include:

- change of Responsible Person
- use of new equipment for an authorised process
- a new contract is signed with new subcontractors, or a new agreement with a collecting centre
- transfer of one or all of the activities to new premises
- cessation of activities or site closure
- a new IT system is implemented

Each CA to insert relevant instructions for submission

Annex II

GUIDE FOR AUDITING TISSUE ESTABLISHMENTS

GUIDE FOR AUDITING TISSUE ESTABLISHMENTS

A. GENERAL POLICIES

A.1 LEGAL AND REGULATORY FRAMEWORK

Does the TE keep copies of the laws, regulations and/or guidelines it follows?

Yes No N/A

Does the TE have an established clear organizational structure?

Yes No N/A

Are clinical and quality system responsibilities defined?

Yes No N/A

Is the Quality System clearly described?

Yes No N/A

Auditor Comments: _____

A.2 STANDARD OPERATING PROCEDURES (SOPs)

Is there a set of authorised Standard Operating Procedures (SOPs) which define the responsibilities?

Yes No N/A

Do they describe how procedures should be carried out and by whom?

Yes No N/A

Where relevant, do the SOPs include, but are not limited, to the following?

- Standard procedures for donor screening/eligibility, consent, retrieval, processing, preservation, packaging, labelling, testing, storage, release and transportation/distribution, or disposal.

Yes No N/A

- Quality Assurance and quality control policies.

Yes No N/A

- Laboratory procedures for tests performed

Yes No N/A

- Specifications for materials used including supply, reagents, storage media, packaging materials.

Yes No N/A

- Personnel and facility safety procedures.

Yes No N/A

- Standard procedures for facilities maintenance, cleaning and waste disposal procedures.

Yes No N/A

- Methods for verification of the effectiveness of sterilisation procedures.

Yes No N/A

- Equipment maintenance, calibration and validation procedures.

Yes No N/A

- Environmental and microbiological conditions, and the methods used for controlling, testing and

- verification. Yes No N/A
- Physiological and physical test specifications for materials. Yes No N/A
 - Methods for determination of shelf life, storage temperature, and assigning expiry dates of tissues and cells. Yes No N/A
 - Determination of inserts and/or label text. Yes No N/A
 - Policies and procedures for release of tissue for transplantation. Yes No N/A
 - Procedures for adverse events reporting and corrective actions. Yes No N/A
 - Donor/recipient tracking and product recall policies/procedures. Yes No N/A

Auditor Comments: _____

A.3 SPECIFIC ASPECTS OF THE QUALITY SYSTEM

1. Quality System

Does the Quality system:

- Comply with the European Directive requirements? Yes No N/A
- Comply with the national legislation requirements? Yes No N/A
- take into consideration:
 - EATB standards? Yes No N/A
 - GMP requirements applying to tissue banking? Yes No N/A
- Have a set of authorized SOPs? Yes No N/A
- Ensure that work performed is standardized and all steps are traceable? Yes No N/A
- Have written agreements with third contracted parties (applying particularly where a key step of the entire process is carried out by another organization)? Yes No N/A

Auditor Comments: _____

2. Quality Review

Is there an audit system in place for the activities for which accreditation (or other) is required? Yes No N/A

Do trained and competent persons perform the audit in an independently?

Yes No N/A

If there are deviations from the required standards of quality and safety, are there documented investigations, including corrective and preventive actions?

Yes No N/A

Does the TE have processes in place for the review of the performance of the quality management system? Yes No N/A

Auditor Comments: _____

A.4 DATA PROTECTION AND ANONYMITY

Is the law and other regulations/guidelines applied present and in SOPs?

Yes No N/A

Do procedures correspond with 95/46/EC and with any additional national regulations?

Yes No N/A

Is there a system for the control of passwords in place? Yes No N/A

Is there a system for the management of password renewal in place? Yes No N/A

Is donor and recipient data to which third parties have access rendered anonymous?

Yes No N/A

Is the identity of the recipient revealed to the donor or his/her family, or vice versa?

Yes No N/A

Is there a procedure in place for the resolution of data inconsistencies?

Yes No N/A

Auditor Comments: _____

A.5. TRACEABILITY

Is there an effective and accurate system in place that ensures unique identification of tissues throughout the banking process, from receipt to distribution? Yes No N/A

Is there a system of vigilance and a procedure for recall and adverse events/reactions available? Yes No N/A

Do the actions taken include tracing of all relevant tissues, and where applicable, include trace-back (to identify donor causing the reaction in the recipient)? Yes No N/A

Does this procedure contain at least the process to trace data:

- From the tissue to the full donor records (including medical and behavioural history, testing, procurement and release) Yes No N/A
- Throughout processing and storage (including identification of equipment and reagents used) Yes No N/A
- From the recipient to the donor-(tissue) Yes No N/A
- From the tissue at risk to all other distributed tissues from the same donor, and/or the same batch? Yes No N/A
- Are the names of the medical facilities and the recipients available? Yes No N/A

Is the information set in Annex VI of Directive 2006/86/EC kept by the TE?

Yes No N/A

Is traceability supported by adequate labelling?

Yes No N/A

Is traceability supported by adequate computer systems?

Yes No N/A

Does the end-user provide the TE a follow-up form on the reception and transplantation of tissues?

Yes No N/A

Auditor Comments: _____

A.6. PERSONNEL TRAINING AND QUALIFICATION

Level of personnel is defined?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
If necessary, is the possession of diplomas per function defined?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
Are there training manuals available for the personnel?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
Does the Quality System see to the following?:	
• A procedure to check whether new personnel to be hired fulfil the criteria set for that specific function	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
• Idem for personnel already under contract, when changing a function	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
• A procedure to work in personnel into a new function (retraining)	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
• An induction procedure that contains information and education	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
• A continuous educational process and budget for education of personnel at different levels	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
• Adequate personnel files with copies of required diplomas and educational history.	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
• Is on-the-job training documented?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
• Is competence of each TE member documented?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>

Auditor Comments: _____

A.7 HEALTH AND SAFETY; COMPLIANCE WITH LEGAL REQUIREMENTS

1. Display of Health and Safety member state law and contacts

H&S law displayed, according to national regulation	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
H&S notices displayed	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
Access to Occupational Health services	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
Access to confidential care services	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>

2. Specific training given to staff regarding health and safety

Staff induction includes basic H&S training	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
Advanced training in specific areas of practice	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>

3. Risk assessments carried out for activities undertaken.

Risk assessments performed; general, substances, manual handling, computer screen working etc. Yes No N/A

Assessments reviewed on a regular basis Yes No N/A

New practices include review of risk assessments Yes No N/A

Particular arrangements in place for young, pregnant, disabled workers/visitors Yes No N/A

4. Evidence of risk reduction in place.

SOPs include steps to safer practice Yes No N/A

Actions to reduce risk identified in risk assessments undertaken Yes No N/A

Code of practice for laboratory working including clothing policy etc. Yes No N/A

Risk assessment conducted prior to contractor working Yes No N/A

5. Caution signage where appropriate

Fire routes clearly signed Yes No N/A

Fire extinguishers present, fire doors closed Yes No N/A

Hazardous equipment/substances signage Yes No N/A

PPE signage where appropriate Yes No N/A

Restricted access to risk areas where required Yes No N/A

6. PPE available for staff and in use

PPE (lab coats/gloves/masks, etc.) available for staff and visitors Yes No N/A

7. Specific monitoring and controls for nitrogen storage where appropriate.

Specific nitrogen room working procedure/policy Yes No N/A

Room oxygen monitors Yes No N/A

Personal oxygen alarms Yes No N/A

Restricted access in the event of alarm Yes No N/A

Nitrogen shutdown procedure Yes No N/A

Breathing apparatus available if room accessed in alarm status Yes No N/A

Specific documented staff training in nitrogen working Yes No N/A

Auditor Comments: _____

A.8. PACKAGING AND LABELLING

1. Packaging

Are all packages and containers validated as fit for purpose?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
Are all labels validated as fit for purpose?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
Is there control of packaging and labels as critical products?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
Is packaging specified in product specification, if relevant?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
Are contingencies validated for use in the event of supply fail?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
Are methods to test and sterilize containers and packages described in SOPs?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
Are products preserved and stored safely, as described in SOPs?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
Does the TE keep the tissue at the required temperature during the defined period of time (are preservation conditions guaranteed)?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
Is the packaging capable of maintaining integrity, quality, function and sterility of the product?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
Is the strength and impact resistance of the packaging and labelling adequate for the storage and transport methods used?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
Are tissues packaged using a standard method, if relevant?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
Are packaged tissues shipped in containers that are suitable for the transport of biological materials and which maintain their safety and quality?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>

Auditor Comments: _____

2. Labelling - General

Are correct labels and labelling used for tissue identification, as defined in SOPs?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
Does labelling comply with data protection and anonymity, and traceability?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
Does labelling show essential information such as “dry ice”, “this side up”, “handle with care”, “human tissue for transplantation”...	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>

Is the label resistant to water? Yes No N/A

During donation and procurement, are accompanying tissue or blood samples for testing (if any) accurately labelled? Yes No N/A

Does the sample label include a record of the time and place the specimen was taken? Yes No N/A

Auditor Comments: _____

3. Procurement Container

Is each tissue segment packaged individually as soon after retrieval as possible, using sterile containers? Yes No N/A

Are appropriate reagents or preservation solutions used, as specified in SOPs? Yes No N/A

Is integrity of the container maintained after filling and closing it? Yes No N/A

Is labelling of tissues or blood samples accurate and does it include a record of the time and place the specimen was taken? Yes No N/A

At the time of retrieval, is every package containing tissue labelled with at least the following data:

- Donor and donation identification/code Yes No N/A
- Type of tissue Yes No N/A
-

Do the container labels comply with additional requirements established by common carriers or by Inter-governmental, national, regional, and local regulation or law? Yes No N/A

Are transportation conditions defined, secured and validated? Yes No N/A

Do selected transport companies fulfil these criteria? Yes No N/A

Auditor Comments: _____

4. Fit-for-use products are labelled with (primary packaging):

- | | |
|--|---|
| • Product, unique ID number/code or batch/lot number/code | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • TE name, address and phone number | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • Expiry date | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • If applicable, autologous and patient identifiers | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • If applicable, patient identifiers for directed use | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • If applicable, Biological hazard if positive for infectious disease. | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |

Auditor Comments: _____

5. Fit-for-use products are labelled with (packaging or accompanying documentation):

- | | |
|--|---|
| • Description and dimensions | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • If applicable, morphology/functional data | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • Date of distribution | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • Biological determinations and results | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • Storage recommendations | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • Opening/handling/reconstitution instructions | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • Expiry after opening | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • Mechanism for adverse event reporting | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • Presence of harmful residues | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |

Auditor Comments: _____

6. Shipping container is labelled with:

- | | |
|---|---|
| • Name, address and phone number of shipping facility | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • Name, address, phone number and contact person of intended receiving facility | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • Statements “Containing Human Tissue” and “Handle with Care” | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • Date and time of start of transportation | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • Recommended transport conditions | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • Safety instructions and method of thawing when applicable | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • “for autologous use only” label in case of autologous donors | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • Biological hazard warning, if applicable | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |

Auditor Comments: _____

A.9 RECORDS AND REGISTERS

Does the TE have a system in place for defined and effective documentation, correct records and registers, and authorised SOPs? Yes No N/A

Does the system in place ensure that all work performed is standardised and that all steps are traceable? Yes No N/A

Are the forms standardised and do they respect local conditions and regulations?

Yes No N/A

Are all the following steps/activities adequately recorded?

- coding Yes No N/A
- donor suitability Yes No N/A
- procurement Yes No N/A
- processing Yes No N/A
- preservation Yes No N/A
- storage Yes No N/A
- transport Yes No N/A
- distribution or disposal. Yes No N/A
- quality control and assurance Yes No N/A
- personnel training and competence Yes No N/A
- facility maintenance and management Yes No N/A

Is there a document control procedure? Yes No N/A

Are the changes to documents periodically reviewed? Yes No N/A

Does the recipient register respond to the following criteria?

- Separated from donor file Yes No N/A
- Anonymous traceability data Yes No N/A
- Name of physician in charge Yes No N/A
- Name of ordering person Yes No N/A
- Name of hospital, department, and ward of hospital of end user Yes No N/A
- Name, personal identification data of recipient (if available) Yes No N/A
- If available, purpose/disease, implantation location of the graft Yes No N/A
- Archiving for 30 years, Yes No N/A

Are all records:

- | | |
|---|---|
| • regarded as privileged and confidential | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • legible and indelible | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • maintained so as to ensure their integrity and preservation | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • able to identify the person responsible for each step | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • include dates | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • show test results and interpretation | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • determine lot numbers and manufacturer of supplies and reagents used. | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • kept in order to ensure access to the data for at least 30 years after expiry date, clinical use or disposal, or in accordance with applicable intergovernmental, national, regional or local law or regulation | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |

Auditor Comments: _____

PART B: TISSUE DONATION

B.1 DONOR SELECTION AND EVALUATION

1. General

Is donor selection and evaluation performed by trained personnel? Yes No N/A

Are there SOPs for the verification of the assessment of the selection criteria for donors?

Yes No N/A

Auditor: Check Reference

Is there a person responsible for donor selection and evaluation? Yes No N/A

Does an authorized person collect all donor documentation needed? Yes No N/A

For living donors, is an interview conducted? Yes No N/A

Is a questionnaire used during this interview? Yes No N/A

For deceased donors, are the cause, time, and circumstances of death observed by the facility? Yes No N/A

Auditor: Verify with Donor documentation.

Is a donor age criteria established, documented and recorded? Yes No N/A

Auditor Comments: _____

2. Donor identity

Is donor identification *detailed in and in accordance with* SOPs? Yes No N/A

Is there a person responsible for the donor identification? Yes No N/A

Is donor identification confirmed and recorded? Yes No N/A

Auditor Comments: _____

3. Donor Consent Details

Are there SOPs for the verification of donor or donor family consent? Yes No N/A

Is there an authorized person that confirms and records that the consent has been obtained in accordance with the legislation in place in your Member State?

Yes No N/A

Verify that the facility has consents required by local regulations and legislation.

Yes No N/A

For living donors, does the informed consent include notification of all reasonable risks, potential harm, and tests to be performed? Yes No N/A

Is the request for donation explained in understandable terms by a health care professional familiar with the donation process? Yes No N/A

Is informed consent obtained in accordance to procedures? Yes No N/A

Auditor Comments: _____

4. Medical History Requirements

Donors are generally excluded from donation if any of the following conditions exists:

Deceased donors:

- Unknown cause of death, unless autopsy provides information on the cause of death after procurement and none of the general criteria for exclusion below applies Yes No N/A
- Past history of a disease of unknown aetiology. Yes No N/A
- Presence or previous history of malignant disease (except primary basal cell carcinoma, carcinoma in situ of uterine cervix, and some primary tumors of the CNS) yes No N/A
- Risk of transmission of disease caused by prions, including Creutzfeldt-Jakob disease, rapid

- progressive dementia or degenerative neurological disease, recipients of hormones derived from human pituitary gland and recipients of grafts of cornea, sclera and dura matter, and persons undergone undocumented neurosurgery). Yes No N/A
- Systemic bacterial, viral or fungal infections not controlled at time of donation, or significant local infection in tissues to be donated. Yes No N/A
 - History, clinical evidence or confirmed positive laboratory tests for HIV infection, acute or chronic hepatitis B or hepatitis C infection or HTLV I/II infection, or history of risk factors for these infections. Yes No N/A
 - History of chronic, systemic autoimmune disease that could have a detrimental effect on the quality of the tissue to be retrieved Yes No N/A
 - Presence or sufficient haemodilution of donor blood samples to make testing invalid and also due to treatment with immunosuppressive agents Yes No N/A
 - Evidence of any other risk factors for transmissible diseases on the basis of a risk assessment, taking into consideration donor travel and exposure history and local infectious disease prevalence. Yes No N/A
 - Presence in donor's body of physical signs implying a risk of infection with transmissible disease(s) Yes No N/A
 - Ingestion of or exposure to a substance that may be transmitted to recipients in a dose that could endanger their health Yes No N/A
 - Recent history of vaccination with a live attenuate virus where a risk of transmission is considered to exist Yes No N/A
 - Transplantation with xenografts Yes No N/A
 - Children less than 18 months old born from mothers with HIV infection, hepatitis B, C or HTLV infection, or at risk of such infection, and who have been breastfed by their mothers during the previous 12 months, cannot be considered as donors regardless of the result of the analytical test (excluded as donors until risk of transmission of infection is definitely ruled out.) Yes No N/A
 - Children born from mothers with HIV infection, hepatitis B, C or HTLV infection, or at risk of such infection, and who have NOT been breastfed by their mothers during the previous 12 months and for whom analytical tests, physical examinations and reviews of medical records do not provide evidence of HIV, hepatitis B, C or HTLV infection, can be accepted as donors. Yes No N/A
 - Additionally for living donors, exclusion if the donor is a mother breastfeeding or pregnant (except for donors of umbilical cord blood cells and amniotic membrane Yes No N/A

Auditor Comments: _____

5. Assessment of Behavioural Risks

Is there a questionnaire in which information regarding the donor's behavioural attitude (increasing risk of transmissible diseases) is recorded? Yes No N/A

Is the person answering medical, social and sexual inquiries about the donor eligible to do so? Yes No N/A

Auditor Comments: _____

6. Physical Examination Requirements

Are cadaveric donors subject to a physical examination prior to retrieval? Yes No N/A

In the *physical examination form*, are key points always answered (never blank)?

Yes No N/A

When the answer is "Yes" (in the form), is an explanation given?

Yes No N/A

Is the body examined to detect any signs that may be sufficient in themselves to exclude the donor?

Yes No N/A

Verify that special attention is given to the following:

- | | |
|---|---|
| ▪ Tumours | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| ▪ Infections | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| ▪ Risk factors for transmissible diseases | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| ▪ Traumas to donor's body | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| ▪ Scars from recent or old operations | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |

Auditor Comments: _____

7. Assessment of Testing results

Does the facility have and comply with SOPs for the assessment of laboratory tests required for donors? Yes No N/A

Are donor's next of kin or physician notified in accordance with state laws of confirmed positive results having clinical significance? Yes No N/A

Are confirmed positive donor infectious disease tests reported to health authorities?

Yes, local health authority Yes, national health authority No N/A

How does the notification proceed for living donors and for cadaveric donors?

Living donors: _____

Cadaveric donors: _____

Auditor Comments: _____

B.2 DONOR CODING

Does the donor selection and evaluation staff allocate a unique identification code to the donor?

Yes No N/A

Is a unique European identifying code allocated to all donated material at the TE?

Yes No N/A

Does the code incorporate at least the following information?

- Unique ID number Yes No N/A
- Identification of the TE (and country/city) Yes No N/A

Auditor Comments: _____

B.3 DONOR TESTING

1. Transmissible Diseases Blood Testing and Microbiological Testing of Donor

Is tissue donor testing for transmissible microbiological diseases in compliance with a law or practice in the country?

Yes No N/A

Is donor testing performed by a qualified laboratory, accredited or authorized as a testing centre by the competent authority ?

Yes No N/A

Is the type of test used validated for the purpose in accordance with current scientific knowledge?

Yes No N/A

Are algorithms in place and are they followed in the case of positive testing results in certain parameters?

Yes No N/A

Are the following serological tests performed for all donors (minimum requirement)?

- HIV Antibodies 1 and 2 Yes No N/A
- HBs-Ag Yes No N/A
- HBcAb (total) Yes No N/A
- HCV-Ab Yes No N/A
- Syphilis: specific treponemal test (e.g. TPHA, TPPA) Yes No N/A

Are serological tests performed on donor's serum or plasma? Yes No N/A

For deceased donors, are blood samples obtained prior to death, or if not possible, within twenty-four hours of death? Yes No N/A

For living donors, are blood samples obtained at the time of donation? Yes No N/A

If not possible, are they obtained within 7 days post donation? Yes No N/A

Is remaining donor serum securely sealed and stored frozen in a proper manner? Yes No N/A

If yes, is there a record that states for how many years it will be stored, after the expire date of the tissue? (recommended, although not required) Yes No N/A

Are additional necessary blood tests performed? Yes No N/A

Auditor Comments: _____

B.4 DONOR DOCUMENTATION

Does the TE keep donor registers? Yes No N/A

Does it archive them for a period of at least 30 years? Yes No N/A

Does each donor have a unique record? Yes No N/A

Does the donor record/form include?

- Donor identification (identification procedure) Yes No N/A
- Age Yes No N/A
- Sex Yes No N/A
- Cause of death Yes No N/A
- Medical and social history (sources of info. and data lacking) Yes No N/A
- Clinical data (haemodilution formula – time and date of sampling) Yes No N/A
- Consent form Yes No N/A
- Body examination results (drawing, correlation between body examination and medical/social history) Yes No N/A
- Procurement results (date and time of retrieval of each tissue) Yes No N/A
- Haemodilution formula Yes No N/A
- Laboratory (and other) test results (time and date of sampling) Yes No N/A
- Autopsy/biopsy results, if applicable (time and date) Yes No N/A

Are data protection and confidentiality measures in place, according to Article 14 of Directive 2004/23/EC? Yes No N/A

Are they legible and permanent? Yes No N/A

Are donor's clinical records maintained for at least 30 years? Yes No N/A

Auditor Comments: _____

PART C: TISSUE PROCUREMENT

C.1 GENERAL PRINCIPLES

1. SOPs for procurement

Does the facility have SOPs for:

- The verification of donor identity? Yes No N/A
- The confirmation of donor/donor family consent? Yes No N/A
- Assessment of donor eligibility? Yes No N/A

Do the SOPs describe the procedures for procurement?

Yes No N/A

2. Informed Consent

Before tissue retrieval, is informed consent ensured by staff and documented?

Yes No N/A

3. Donor Identification and Coding

Do retrieval staff verify positive donor identity?

Yes No N/A

Is there a system in place for the identification of human tissues and cells?

Yes No N/A

Is a unique European identifying code allocated to all donated material at the TE, if such a coding exists?

Yes No N/A

Does the facility ensure that a unique donor identification number is assigned to each donor?

Yes No N/A

Does the code incorporate at least the following information:

- Donation identification:
 - Unique ID number Yes No N/A
 - Identification of the TE (and country/city) Yes No N/A
- Product identification:
 - Product code (basic nomenclature) Yes No N/A
 - Split number (if applicable) Yes No N/A
 - Expiry date Yes No N/A

Auditor Comments: _____

C.2 RETRIEVAL CONDITIONS

1. General. Time limits

Are tissue procurement methods described in sufficient detail in SOPs?

Yes No N/A

Are all procurement procedures validated?

Yes No N/A

For living donors, does procurement occur in an environment that ensures their health, safety and privacy?

Yes No N/A

Is procurement personnel adequately trained to retrieve tissues within specified time limits?

Yes No N/A

Does the SOP manual indicate the time limits for post-mortem retrieval of tissues?

Yes No N/A

Do staff adhere properly to time limits?

Yes No N/A

Is there a policy for cases where retrieval is delayed for cadaveric donors?

Yes No N/A

2. Facilities

Do qualified and trained personnel perform procurement in qualified and appropriate facilities?

Yes No N/A

Are the environmental conditions of these facilities adequate and as described in SOPs?

Yes No N/A

3. Equipment

Are single-use instruments utilized during procurement?

Yes No N/A

If no, are all instruments and equipment sterilized between procurements, according to a validated method?

Yes No N/A

Check lot number and expiry date of equipment, reagents and mediums.

4. Retrieval techniques and Prevention of Contamination

Throughout the procurement procedure, is aseptic technique observed?

Yes No N/A

During aseptic procurement, are procurement sites prepared using a standard surgical practice?

Yes No N/A

Are all methods consistent with standard operating room practice? Yes No N/A

During clean non-sterile procurement, are efficient validated sterilizing methods used to eliminate pathogens after retrieval? Yes No N/A

Note: in this case, allografts are suitable for transplantation.

Does TE ensure that tissues are not contaminated during the retrieval?

Yes No N/A

For living donors, are tissues removed under conditions that represent the least possible risk to the donor, and in properly equipped and staffed institutions? Yes No N/A

Auditor Comments: _____

5. Microbiological testing of tissues retrieved

If samples for microbiological cultures are obtained at the time of retrieval, are samples of each retrieved tissue taken prior to exposure of the tissue to antibiotic or antiseptic containing solution? Yes No N/A

Verify that the date and time of sampling is recorded.

Does the culture technique allow the growth of both aerobic and anaerobic bacteria and fungi? Yes No N/A

Are these testing results documented in the donor record? Yes No N/A

Are there established bacteriological bioburden limits for tissue samples for permitted tissue distribution, regarding the degree of virulence of the microorganisms found on the samples, if any? Yes No N/A

6. Body Reconstruction of cadaveric donors

Does the facility maintain a procedure for donor reconstruction? Yes No N/A

Is the donor's body reconstructed as closely as possible to its original anatomical shape? Yes No N/A

Do the SOPs and the trained staff that donor reconstruction will be done properly?

Yes No N/A

Does the facility maintain records on donor's final disposition?

Yes No N/A

Does the facility maintain records on donor's final disposition (applicable for TEs having their own morgue/retrieval facilities?)

Yes No N/A

Auditor Comments: _____

C.3 RETRIEVAL DOCUMENTATION

1. General – Procurement Records

Are appropriate records of each donation procedure and of all tissues retrieved available and kept by the tissue bank?

Yes No N/A

Do these standardized forms respect the local conditions and regulations?

Yes No N/A

Are the forms filled and signed by designated procurement team members?

Yes No N/A

Are they checked and signed by responsible person or his/her assignee?

Yes No N/A

2. Documentation

Verify that all retrieved tissues are provided with an accompanying form including the following minimal information:

- Identification, name and address of the TE to receive the tissues/cells

Yes No N/A

- Donor identity (including how and by whom the donor was identified)

Yes No N/A

- Date, time (where relevant, start and end) and place of procurement and procedure used. Where relevant, environmental conditions at the procurement facility

Yes No N/A

- Identity of the person(s) performing the retrieval

Yes No N/A

- Identity and signature of the responsible procurement officer

Yes No N/A

- Description and identification of tissue(s)/cells retrieved (including samples for testing) Yes No N/A
- For deceased donors, conditions under which the cadaver is kept(refrigerated or not, time of start and end of refrigeration) Yes No N/A
- ID/batch numbers of reagents and transport solutions used Yes No N/A
- Date and time of death where possible Yes No N/A
- Date and time of procurement may be included, where possible Yes No N/A
- Details of the physical examination form prior to retrieval, in case of deceased donors Yes No N/A
- Where sperm is procured at home, the procurement report must state this and must contain only the name and address of the TE to receive the tissues/cells, and the identification of the donor Yes No N/A

Auditor Comments: _____

C.4 TRANSPORTATION TO TE

Is the transportation provided under conditions that minimize the risk of contamination and that guarantee the retainment of the biological properties of the tissues procured?

Yes No N/A

Are these conditions specified in the SOPs and are they validated? Yes No N/A

Are procedures used to ensure and document proper temperature storage during transit?

Yes No N/A

Has the contracted facility validated the packaging and transport conditions (temperatures) of frozen tissue shipped to the tissue bank? Yes No N/A

If shipping container validation has not occurred, are there policies for the method of temperature monitoring? Yes No N/A

Auditor Comments: _____

PART D: TISSUE PROCESSING

D.1 GENERAL PRINCIPLES

1. Tissue Processing prepared according to SOPs

1.1. All processes will be carried out to validated, authorised SOPs that clearly describe the process and expected outcome.

Do all processes have a documented and approved SOP? Yes No N/A

Do SOP's state their intended purpose, are they available to staff. Yes No N/A

Is there evidence SOPs are validated prior to implementation? Yes No N/A

Is there evidence that staff is only working to the described procedures?
Yes No N/A

1.2. The Quality system will control the version in use and evaluate its current validity (review).

A document control procedure includes:

• SOP to control documents. Yes No N/A

• Authorisation (Manager/Quality) system for documents. Yes No N/A

• Minimum review period with evidence of compliance. Yes No N/A

• System of ensuring the correct version is in use with evidence.
Yes No N/A

1.3. There will be staff training records to demonstrate staff continued competence and compliance to SOPs.

All staff have training records linked to SOPs Yes No N/A

All staff is assessed as competent and authorised to undertake a procedure before carrying it out. Yes No N/A

There is evidence of ongoing competence monitoring. Yes No N/A

Auditor Comments: _____

2. Unique tissue identification number

2.1 The bank shall have a unique coding system with minimum dataset comprising:

- | | |
|-----------------------------------|---|
| • Unique donor identification | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • ID of tissue establishment | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • Product code | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • Pack/Split number if applicable | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • Expiry date | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |

Are there mechanisms to ensure codes are only assigned to the appropriate tissues and cannot be mixed?

Yes No N/A

Are subsequent donation events linked?

Yes No N/A

How does the establishment guarantee it is internationally unique?

Auditor Comments: _____

3. Reception policies of retrieved tissues at the processing/storage establishment.

Does the shipment meet the specifications of the receiving establishment?

Yes No N/A

Is there documented verification of this?

Yes No N/A

Is all tissue material tested according to the required testing regime?

Yes No N/A

Is there a procedure to separate quarantine from “approved tissue”?

Yes No N/A

Is the outside integrity of the package intact upon arrival?

Yes No N/A

Auditor Comments: _____

4. Validation of the methods applied

4.1. All processes will be validated (locally, published or retrospective evaluation) for

effectiveness against the desired outcome.

Does change control include validation steps to demonstrate desired outcome?

Yes No N/A

Are validations will approved by the Responsible Person or approved designate?

Yes No N/A

Where long standing historic processes are not validated, is there documented retrospective evaluation or published data to demonstrate validity of the process.

Yes No N/A

4.2. Where a defined specification limit is required, e.g. moisture level, this will be assessed and recorded.

Where a process requires specified parameters, e.g. temperature, each process will be validated to routinely achieve the desired parameter:

- Controlled freezing rate Yes No N/A
- Freeze drying Yes No N/A
- Other (state) _____ Yes No N/A

Are parameters checked as part of normal authorisation? Yes No N/A

4.3 Staff will be assessed for aseptic working (where appropriate) using simulation qualification (e.g. media fill).

Has aseptic working been validated by all staff e.g. by media fill? Yes No N/A

Auditor Comments: _____

5. Pooling

5.1. Avoidance of cross-contamination.

Do staff only work with one batch at a time? Yes No N/A

Is there a clean down between each batch? Yes No N/A

Where batches are manipulated in the same environment is there evidence that cross contamination risk has been considered and minimised? Yes No N/A

Does multiple donor pooling occur? Yes No N/A

Justification:

Auditor Comments: _____

6. Control and recording of key parameters (e.g. cooling curves, freeze-drying cycles)

6.1 Key parameters will be recorded and documented to calibrated standards and approved as part of product release.

Where a process requires specified parameters each process will have documented proof of conformance to validate/approve each process.

- | | |
|-----------------------|---|
| • Temperature | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • Moisture | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • Other (state) _____ | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |

Auditor Comments: _____

7. Specific Processing Procedures

It must be demonstrated that processes applied will not adversely affect the clinical performance of the graft nor the recipient.

Processes applied are validated for

- | | |
|-------------------------------|---|
| • viability | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • mechanical effects | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • cytotoxicity | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |
| • clinical performance review | Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> |

Auditor Comments: _____

D.2 EQUIPMENT SUITABILITY, STERILITY AND TRACEABILITY

Is there a procedure for identifying and managing critical supplies? Yes No N/A

1. Specifications will be available for all critical equipment and consumables.

Are critical equipment and supplies catalogued? Yes No N/A

Does this catalogue encompass all critical equipment and supplies? Yes No N/A

Does each item have a requirement/acceptance specification? Yes No N/A

2. Consumables and equipment will be quarantined and shown to comply to specification prior to use with supporting evidence recorded.

Has each item being approved for use against specification Yes No N/A

Is there an effective segregated quarantine area for receipt of goods? Yes No N/A

3. Critical equipment will be serviced and maintained to schedule and where appropriate be validated and calibrated for use.

Is there a catalogue of maintenance/servicing for all critical equipment?

Yes No N/A

Are there signed, current service agreements defining responsibilities and specifications of work required? Yes No N/A

Is it clear that equipment in use is fit for use? Yes No N/A

Is there a mechanism for ensuring that unsuitable equipment is 'removed' from use?

Yes No N/A

Are validation/calibration records available for critical items? Yes No N/A

Are validation/calibration reports approved/accepted by the tissue bank?

Yes No N/A

4. All processing records will include records or batch numbers with expiry dates of consumables, and equipment logs to demonstrate the kit used with linkage to sterilisation cycles if applicable.

Do processing records include batch numbers and expiry of supplies? Yes No N/A

Do processing records record critical equipment kit used? Yes No N/A

5. Mechanisms must be in place to permit quarantine or recall of tissue exposed to materials subsequently found to be non-conforming.

Are materials used checked for suitability and being in date as part of routine quality monitoring and tissue release? Yes No N/A

Can supplies and equipment be traced in the event of recall? Yes No N/A

Is there evidence that a practice or real tracking exercise been undertaken recently based on a supplies/consumables recall? Yes No N/A

Auditor Comments: _____

D.3 ENVIRONMENTAL CONTROLS

1. Processing and storage areas are kept clean with evidence of cleaning documented

Is there a cleaning policy for controlled and uncontrolled areas? Yes No N/A

Is there a cleaning record for all GMP areas? Yes No N/A

Are the GMP areas clean and tidy (to enable effective cleaning)? Yes No N/A

Auditor Comments: _____

2. Tissues exposed to the environment without terminal microbial inactivation will be processed in GMP air quality grade A.

Are non-terminally sterilised tissues processed in grade A? Yes No N/A

Where a grade B background is not used, is the grade A validated? Yes No N/A

Justification:

Is there evidence staff is regularly trained in GMP aseptic working? Yes No N/A

Is the processing grade qualified for each batch processed? Yes No N/A

Auditor Comments: _____

3. Deviation from GMP grade A above must be specified, validated and justified.

Is the processing environment reviewed against standard? Yes No N/A

Where non-conforming, are tissues segregated to prevent release? Yes No N/A

If released for clinical use, is the rationale documented and independently approved?

Yes No N/A

Is clean room/cabinet performance reviewed and performance trended by the tissue bank and an independent person? Yes No N/A

Auditor Comments: _____

4. Tissues exposed to the environment with subsequent terminal sterilisation will be processed at least in European Directive air quality grade D (best if processed in GMP air quality grade C).

Are terminally sterilized tissues processed in air quality grade D? Yes No N/A

Are terminally sterilised tissues processed in air quality grade C? Yes No N/A

Auditor Comments: _____

5. The effectiveness of equipment and cleaning must be validated and monitored to demonstrate specified limits with no cross contamination.

Are cleaning agents validated for purpose including effectiveness? Yes No N/A

Is the clean room and/or working cabinet certified for use against relevant standards by a qualified person? Yes No N/A

Has practice been independently reviewed to determine risk of contamination and measures taken to mitigate the risk? Yes No N/A

Are products tested to ensure they have not been contaminated? Yes No N/A

Auditor Comments: _____

6. Staff gowning and hygiene must be documented, validated and qualified.

Are staff trained in gowning practice? Yes No N/A

Is there a staff hygiene policy including attire, makeup etc.? Yes No N/A

Are staff regularly qualified for aseptic gowning performance? Yes No N/A

7. Environmental monitoring reviewed as part of product release

Does product release include:

- Cleanroom monitoring including plates, pressures, particles, etc? Yes No N/A
- Cabinet monitoring? Yes No N/A
- Gloveprint monitoring? Yes No N/A
- Product contamination monitoring? Yes No N/A

Does non-conformity include a retrospective review of inventory? Yes No N/A

Auditor Comments: _____

8. Trends analysed and reviewed as part of routine quality review

Are deviations recorded as Quality Incidents? Yes No N/A

Is there trend analysis data with route cause analysis? Yes No N/A

Auditor Comments: _____

D.4 TRACEABILITY OF TISSUE THROUGH PROCESSING

STANDARD:

Donation data kept must include:

- Tissue Establishment or Procurement Organisation
- Unique ID number
- Date and place of Procurement
- Type of donation (allo/auto, living/deceased etc)

Product data kept must include:

- Tissue Establishment responsible
- Type of product
- Batch/Pool if applicable
- Split if applicable
- Expiry date
- Status (e.g. quarantine/fit for use)
- Description of process, materials and additive lot numbers
- Date and location of distribution/disposal

AUDIT GUIDANCE:

Select 4 processing reports at random and verify that the donation and product data stated above is included.

1. An effective and accurate system must be defined to ensure unique identification of tissues throughout the banking process from receipt to distribution.

Can tissue be effectively tracked throughout the process? Yes No N/A

Does this include what task was performed by who, when and where?

Yes No N/A

Is a traceable tissue storage inventory kept (current and retrospective)?

Yes No N/A

Auditor Comments: _____

2. Donation data kept will include as a minimum set:

- Tissue Establishment or Procurement Organisation Yes No N/A
-
- Unique ID number Yes No N/A
-

- Date and place of Procurement Yes No N/A
 - Type of donation (allo/auto, living/deceased etc) Yes No N/A

Auditor Comments: _____

3. Product data kept will include as a minimum set:

- Tissue Establishment responsible Yes No N/A
 - Type of product Yes No N/A
 - Batch/Pool if applicable Yes No N/A
 - Split if applicable Yes No N/A
 - Expiry date Yes No N/A
 - Status (e.g. quarantine/fit for use) Yes No N/A
 - Description of process, materials and additive lot numbers Yes No N/A
 - Date and location of distribution/disposal Yes No N/A

Auditor Comments: _____

D.5 MICROBIOLOGICAL TESTING OF FINAL TISSUE

1. There will be an evidenced/risk-based release policy on microbiology including sampling methodology and exclusion criteria:

- Policy in place for release criteria regarding bacterial, fungal and spore contamination of grafts. Yes No N/A
 - SOPs for sampling Yes No N/A
 - Risk assessment for methodology used for sampling Yes No N/A

2. Tissues not terminally sterilised will be sampled just prior to final packaging.

Sampling occurs at time critical points in the process

- Pre final packaging for non sterilised grafts

Yes No N/A

3. Retrieved tissue gross contamination will be assessed as an exclusion criteria.

Sampling occurs at time critical points in the process

- Pre process
- Pre final packaging for non sterilised grafts

Yes No N/A
Yes No N/A

4. Test results or methodology will be approved by a Microbiologist.

Process and validation approved by qualified Microbiologist

Yes No N/A

Accountability is via a registered practitioner in Microbiology

Yes No N/A

5. Review of microbiology results prior to tissue release

Is there a review of the microbiology test results before the tissue is released?

Yes No N/A

Auditor Comments: _____

D.6 ADVERSE EVENT MANAGEMENT

Does the TE have a system for the detection, evaluation, documentation and reporting of errors and adverse events? Yes No N/A

Does the TE have a system for corrective and preventive actions? Yes No N/A

Are corrective actions documented, initiated and completed in a timely and effective manner? Yes No N/A

Are preventive and corrective actions assessed for effectiveness after implementation?

Yes No N/A

Auditor Comments: _____

PART E: TISSUE STORAGE

E.1 GENERAL PRINCIPLES

1. Validation of containers and packaging materials

1.1 Transport packaging/containers must be validated fit for use, specified and treated as a critical item.

All transport packaging validated fit for purpose Yes No N/A

Control of transport containers as critical products Yes No N/A

Volume of coolants validated and specified in SOPs Yes No N/A

2. Clear separation between tissues available for distribution and in quarantine.

2.1 Quarantined and fit for transplant tissues segregated Yes No N/A

2.2 Process flow does not permit mix up between products in different stages of production

Yes No N/A

Auditor Comments: _____

E.2 STORAGE CONDITIONS

Control of relevant physical conditions (e.g. temperature)

- Continual alarmed temperature monitoring Yes No N/A
- Full audit of inventory against its temperature history Yes No N/A
- Storage equipment validation prior to release into use and following repairs. Yes No N/A
- Temperature mapping of appliance has been carried out Yes No N/A

Auditor Comments: _____

E.3 TISSUE RELEASE

1. Safe system for authorizing and executing the transfer of tissues from quarantine to available for distribution:

Are there:

- SOP for release in place Yes No N/A
- SOP for transfer to clinical use Yes No N/A
- Release includes medical, production and independent quality approval Yes No N/A
- Mechanism for release is approved by the Responsible Person Yes No N/A

2. Expiry Dates established for all tissues released

2.1 Expiry date defined:

- Expiry dates are validated to maintain tissues fit for purpose Yes No N/A
- Expiry times are defined in policy Yes No N/A

2.2 Stock control:

- Inventory is within date Yes No N/A
- Stock is rotated to prevent wastage Yes No N/A
- Stock control policy in place Yes No N/A
- Stock control manages donation activity to maximise use Yes No N/A

Auditor Comments: _____

PART F: TISSUE DISTRIBUTION

F.1 GENERAL PRINCIPLES

Are critical transport conditions, such as temperature and time limit, described in SOPs?

Yes No N/A

Are procedures for the handling of requests for tissues in place?

Yes No N/A

Is there a documented system for the handling of returned products?

Yes No N/A

Does the distribution/allocation policy see to equitable access of recipients to tissues?

Yes No N/A

Are "clients" able to receive and temporarily store tissues under adequate conditions?

Yes No N/A

Auditor Comments: _____

F.2 TRANSPORTATION

Does the TE have selected professional transporters? Yes No N/A

Unless the TE transports tissues itself, does it keep contracts of the professional transporters? Yes No N/A

Is the transport company able to prove that contracted conditions are adequately applied?

Yes No N/A

Is there documented agreement between the TE and the contracted party?

Yes No N/A

Does the transport company correspond with traceability criteria? Yes No N/A

Auditor Comments: _____

F.3 RECEPTION POLICIES AT THE END USER

Does the TE instruct the end user (before the reception of the package) about the time/nature and handling of the transported package? Yes No N/A

Users applying tissues will be required to store data on:

- Supplying establishment Yes No N/A
- End user and facility Yes No N/A
- Product type and identifier Yes No N/A
- Recipient identifier Yes No N/A
- Date of use/disposal Yes No N/A

Auditor Comments: _____

F.4 ADVERSE EVENT/REACTION MONITORING AND RECALL

Is the management of Serious Adverse Reactions/Events and non-conformities (system of vigilance) suitable and described in SOPs? Yes No N/A

Is there an effective recall procedure? Yes No N/A

Is there personnel authorised in the TE to assess the need for recall and to initiate and coordinate necessary actions? Yes No N/A

Does the recall procedure include a description of the responsibilities and actions to be taken (notify the TE without delay of any SAR/E that may influence the quality and safety of tissues)? Yes No N/A

Does the TE provide to the organisation responsible for human application information about how to report SAR/E to them? Yes No N/A

Does the TE have procedures in place to notify the competent authority without delay about suspected SAR/E? Yes No N/A

Does it also communicate all the conclusions of the investigations? Yes No N/A

Are actions taken within pre-defined periods of time? Yes No N/A

Auditor Comments: _____

F.5 WAITING LISTS AND IMPORT/EXPORT POLICIES

Do waiting lists for recipients of each tissue see to fair allocation for each recipient?

Yes No N/A

Is the following criteria observed?

- Medical urgency Yes No N/A
- HLA match Yes No N/A
- Paediatric recipients Yes No N/A
- Physical characteristics of the available graft and the requested transplant criteria for the recipient Yes No N/A
- Country/region of origin of recipient and donor Yes No N/A

- Waiting time

Yes No N/A

Auditor Comments: _____
