EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Public Health and Risk Assessment
**C6 - Health measures**

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# Technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells

## BACKGROUND

In order to ensure a high level of human health protection and to prevent the transmission of diseases by human tissues and cells, the European Parliament and Council adopted Directive 2004/23/EC laying down standards of quality and safety for the donation procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

The Directive 2004/23/ EC applies to donation, procurement, testing, processing, preservation, storage and distribution of human cells and tissues intended for human application and of manufactured products derived from human tissues and cells intended for human applications. Where such manufactured products are covered by other directives, the Directive applies only to donation, procurement, and testing. The Directive does not apply to tissues and cells used as an autologous graft within the same surgical procedure; blood and blood components as defined by Directive 2002/98/EC or to organs or parts of organs if it is their function to be used for the same purpose as the entire organ in the human body.

This Directive calls *inter alia* for the establishment of specific technical requirements related to all the processes from donation to distribution.

On August last year the Commission, which is required by Directive 2004/23/EC to develop these technical requirements, launched a draft document for open consultation which aimed to cover all human cells and tissues and all manufactured products derived from them, which are used for application to the human body, during the first phases of the process – donation, procurement and testing – in order to ensure their quality and safety.

The Commission has prepared a second draft document, presented in this open consultation, addressing the technical requirements for processing, preservation, storage and distribution of human tissues and cells.

This Document incorporates the criteria for accreditation/designation/authorisation/licensing of tissue establishments, including the quality system requirements. It also describes the additional criteria with which Tissue establishments shall comply for the accreditation, designation, authorisation or licensing of tissue and cell preparation processes.

The traceability requirements, the basic characteristics of the EU coding system and the requirements for adverse event reporting are also incorporated..

This document reflects the technical annexes adopted by the Commission in the original proposal for the Directive COM (2002/0319 final). The technical annexes were removed from the Directive text during the legislative process, when the Council and Parliament decided that they should be developed by comitology. In addition the document incorporates the extensive comments and contributions received from a Commission working group of experts, representing the tissue and cell community, including the Council of Europe.

## 1. DEFINITIONS

(a) Quality management system means the organizational structure, defined responsibilities, procedures, processes, and resources for implementing quality management and includes all activities which contribute to quality, directly or indirectly.

(b) Quality management means the co-ordinated activities to direct and control an organisation with regard to quality.

(c) SOPs: Standard Operating Procedures.: written instructions describing the steps in a specific process including the materials and methods to be used and the expected end product.

f) *Critical* means potentially having an effect on the quality and/or safety or having contact with the cells and tissues

(d) *Traceability* means the ability to identify and locate the tissue/cell during any step between its donation, procurement, processing, testing, storage, and distribution, whether to recipient or disposal. It implies the capacity to identify the donor and the tissue establishment, or the manufacturing facility receiving the tissue/cells and, at the medical facility/facilities, the ability to identify the recipient(s). Traceability also concerns all relevant data relating to critical products, equipment and materials.

e) *Validation (or qualification in case of equipments or environments)* means establishing documented evidence that provides assurance that a specific process, 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.

f) *Reporter establishment* means the tissue establishment or the hospital or facility where the application of tissues and cells takes place that reports serious adverse reactions and/or serious adverse events to the competent authority.

## 2. GENERAL CRITERIA FOR ACCREDITATION, DESIGNATION, AUTHORISATION OR LICENSING OF TISSUE ESTABLISHMENTS:

To be accredited, designated, authorised or licensed, a tissue establishment must demonstrate compliance with the following requirements.

### A. Organisation and management

1. A responsible person must be appointed having qualifications and responsibilities as stated in Article 17 of Directive 2004/23/EC.

2. A tissue establishment must have an organisational structure and operational procedures appropriate to the activities for which accreditation / designation / authorisation / licensing is sought; there shall be an organisational chart which clearly defines accountability and reporting relationships.

3. There must be a documented quality management system applied to the activities for which accreditation / designation / authorisation or licensing is sought, in accordance with the standards laid down in this Directive

4. It must be ensured that the risks inherent in the use and handling of biological material are identified and minimised, consistent with maintaining adequate quality and safety for the intended purpose of the tissues and cells The risks include those relating to the procedures, environment, etc. specific to the tissue establishment.

5. There must be documentation defining any agreements that will be maintained with third parties as specified in Article 24 of Directive 2004/23/EC. Third party agreements will specify the terms of the relationship and responsibilities as well as the protocols to be followed to meet the required performance specification.

6. There must be a documented system in place, supervised by the responsible person, for ratifying that tissues and/or cells meet appropriate specifications for safety and quality for release and for their distribution.

7. There must be 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 establishments as specified in Article 21.5 of Directive 2004/23/EC.

8. There must be a documented system in place that ensures the identification of every tissue and/or cell unit at all stages of the activities for which accreditation/designation/authorisation/licensing is sought.

### B. Personnel

1. The personnel in tissue establishments shall be available in sufficient number and be qualified for the tasks they perform. The competency of the personnel shall be evaluated at specified appropriate intervals specified in the Quality System.

2. All personnel should have clear, documented and up-to-date job descriptions. Their tasks, responsibilities and accountability shall be clearly documented and understood, consistent with the requirement detailed in 2.A.1 and 2.A.2.

3. Personnel should be provided with appropriate initial/basic training and continued professional development to carry out the activities for which accreditation / designation / authorisation or licensing is sought, in accordance with the standards laid down in this Directive.

4. The initial/basic and on-going training programme for staff working in the tissue establishments shall be:

   a) Evaluated at the end of a course to demonstrate competency in relevant activities;
   b) Carried out when a new employee, activity or a new technology is introduced; and
   c) Documented, reviewed and updated periodically, but at least every two years, and be adequate to their needs.

5. The training programme shall update the knowledge of the staff on the following subjects:

   General topics:

   a) General overview of the procedures covering the activities for which accreditation / designation / authorisation / licensing is sought;
   b) Legal aspects, including data protection and confidentiality;
   c) Ethical aspects;
   d) Organisational aspects;
   e) Quality management system overview;
   f) Quality and safety criteria standards and principles of good practice applied to the activities for which accreditation / designation / authorisation / licensing is sought; and
   g) Safety at work.

   Specific topics (where relevant for the activities for which accreditation / designation / authorisation / licensing is sought) shall be tailored to the specific tasks of employees and should at least address:

   a) Technical knowledge and specific SOPs
   b) Management of registers and data analysis programmes;
   c) Handling of the equipment;
   d) Knowledge of the quality control procedures and;
   e) Knowledge of the personal safety rules including hygiene requirements and use of personal protective equipment;

**C. Equipment and materials**

1. All equipment shall be designed and maintained to suit its intended purpose and shall minimize any hazard to recipients and/or staff.

2. All critical equipment and technical devices shall be validated, regularly inspected and preventatively maintained in accordance with the manufacturers instructions. All equipment with a measuring function must be calibrated against a traceable standard.

3. New and repaired equipment shall be tested when installed and should be authorised before use. Test results shall be documented.

4. Maintenance, servicing, cleaning, disinfection and sanitation of all critical equipment shall be performed regularly and recorded accordingly.

5. Procedures for the operation of each piece of critical equipment, detailing the action to be taken in the event of malfunctions or failure, shall be available.

6. The procedures for the activities for which accreditation / designation / authorisation / licensing is sought, shall detail the specifications for critical materials and reagents. In particular, specifications for additives (e.g. solutions) and packaging materials shall be defined. Critical reagents and materials shall meet documented requirements and specifications and when applicable the requirements of the relevant Directives, namely Directive 98/79/EC on in vitro diagnostic medical devices and 93/42 on Medical Devices**.**

7. Where equipment or materials affect critical processing or storage parameters (e.g. temperature, pressure, particle counts), these parameters shall be identified and shall be the subject of appropriate monitoring and corrective action, as required. to ensure that critical parameters can be maintained within acceptable limits in the event of a malfunction.

**D. Facilities / premises**

1. A tissue establishment must have suitable facilities to carry out the activities for which accreditation / designation / authorisation or licensing is sought, in accordance with the standards laid down in this Directive.

2. When these activities include processing of tissues and cells, this shall take place in an environment with specified air quality and cleanliness in order to minimise the risk of contamination, particularly cross-contamination between samples. The effectiveness of these measures shall be validated and monitored.

3. Unless otherwise specified (see point 4) where tissues or cells are exposed to the environment during processing, without a subsequent microbial inactivation process, an air quality of Grade A as defined in the current European Guide to Good Manufacturing Practice, Annex 1 (Commission Directive 2003/94/EC).) is required, usually achieved by using a laminar air flow (LAF) cabinet. The background environment must be demonstrated to guarantee the maintenance of Grade A in the tissue/cell manipulation area while in use and unmanned.

4. A less stringent environment may be acceptable where:

   (a). A validated microbial inactivation or terminal sterilisation process is applied after final packaging;

(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 bacterial or fungal infection than cell and tissue transplantation (e.g. insemination);

(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).

In (a) above, an environment of at least Grade C shall be provided. In the other circumstances listed, an environment shall be provided that is as close as possible to Grade A, given the constraints described, and it shall be demonstrated and documented that it achieves the quality and safety required for the intended purpose of the tissues and cells.

5. Appropriate garments and equipment for personal protection and hygiene shall be provided in each relevant department of the tissue establishment along with written hygiene and gowning instructions.

6. 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, must be defined.

7. Critical parameters (e.g. temperature, humidity, potential contamination) must be controlled, monitored, and recorded to demonstrate compliance with the specified storage conditions.

8. Physically separate areas should be provided for the storage of tissues and cells prior to release / quarantine, and for released and for rejected tissues and cells. A separate area should be allocated in both quarantine and released storage locations for certain tissues and cells collected in compliance with special criteria (e.g., Autologous or Directed Donations and known infected materials).

9. The areas in which cells/tissues are stored shall be accessible only to authorized persons.

**E. Documentation and registry**

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 shall be regularly reviewed and shall conform to the standards laid down in this Directive. The system shall ensure that work performed is standardised, and that all steps are traceable; i.e. coding, donor eligibility, procurement, processing, preservation, storage, transport, distribution, including aspects relating to quality control and quality assurance.

2. For every critical activity, the materials, equipment and personnel involved shall be identified and documented.

3. All changes to documents shall be reviewed, dated, approved, documented and implemented promptly by authorised personnel.

4. A document control procedure shall be established to provide for the history of document reviews and adjustments and to ensure that only current versions of documents are in use.

5. Records shall be shown to be reliable and a true representation of the results.

6. Records must be legible and indelible and may be hand-written or transferred to another system, such as a computer or microfilm.

7. All records, including raw data, which are critical to the safety and quality of the tissues and cells, shall be kept so as to ensure access to these data for 30 years after expiry date, clinical use or disposal.

8. Registers must meet the confidentiality requirements laid down in Article 14 of Directive 2004/23/EC. Access to registers and data shall be restricted to persons authorised by the responsible person and the Competent Authority for the purpose of inspection and control measures.

**F. Quality review**

1. An audit system including self-inspections or third party audits shall be in place for the activities for which accreditation / designation / authorisation / licensing is sought. Trained and competent persons should conduct these in an independent way, at least annually, in order to verify compliance with the approved protocols and the regulatory requirements. Findings and corrective actions shall be documented.

2. Tissues and cells that do not meet the required standards of safety and quality, must be labelled and handled accordingly. These product deviations shall lead to documented investigations, which include a decision on possible corrective and preventive actions. The fate of non-conforming tissues and cells must be determined in accordance with written procedures supervised by the Responsible Person and recorded. All affected tissues and cells shall be identified and accounted for.

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

4. The tissue establishment should have processes in place for review of the performance of the quality management system to ensure continuous and systematic improvement

5. Inter-institutional audits and quality assurance schemes shall be promoted and encouraged.

## 3. CRITERIA FOR ACCREDITATION, DESIGNATION, AUTHORISATION, LICENSING OF TISSUE AND CELL PREPARATION PROCESSES AT THE TISSUE ESTABLISHMENTS:

In addition to meeting the general requirements for accreditation, designation, authorisation or licensing described in section 2. above, tissue establishments must comply with the following accreditation, designation, authorisation or licensing criteria for the specific activities they carry out.

### A. Reception at the tissue establishment

Reception of procured tissues and cells at the tissue establishment shall comply with the requirements defined in (Commission Directive on donation, procurement and testing).

### B. Processing

When the activities for which the accreditation / designation / authorisation / licensing is sought include processing of tissues and cells, the tissue establishment procedures shall comply with the following criteria:

1. The processing procedures shall be validated and shall not render the tissues or cells clinically ineffective or harmful to the recipient. This validation may be based on previously published studies or, for well established procedures, by retrospective evaluation of the establishment's own data.

2. It has to be demonstrated that the validated process can be carried out consistently and effectively in the tissue establishment environment by the staff, following their written procedures.

3. The procedures shall be documented in SOPs which shall conform to the validated method and to the standards laid down in this Directive, accordingly with points 2.E.1.

4. It shall be ensured that all processes are conducted in accordance with the approved SOPs It shall be ensured that all processes are conducted in accordance with the approved SOPs.

5. When technical procedures cannot be verified at any particular time throughout the process, appropriate parameters must be identified and must be continuously monitored to ensure that the established specifications are met.

6. Where a microbial inactivation procedure is applied to the tissue or cells, it must be specified, documented, and validated.

7. Where any significant change in processing occurs these validation steps must be repeated and documented.

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8. The processes shall undergo regular critical evaluation to ensure that they continue to achieve the intended results.

9. Special procedures shall be implemented for handling of tissue and cells that are to be discarded to prevent the contamination of other tissue/cells, the processing environment or personnel. These procedures shall comply with local regulations.

**C. Storage and release of products**

When the activities for which the accreditation / designation / authorisation / licensing is sought include storage and release of tissues and cells, the authorised tissue establishment procedures shall comply with the following criteria

1. In addition to any national legal requirements in Member States, maximum storage time must be specified for each type of storage condition. The selected period must reflect possible deterioration of the required tissue and cell properties, changing donor selection and testing criteria over time and the availability of alternative treatments.

2. There shall be a system of inventory hold for tissues and/or cells to ensure that they cannot be released until all requirements have been satisfied. There shall be a standard operating procedure that details the circumstances, responsibilities and procedures for the release of tissues and cells for distribution.

3. A system for identification of tissue and cell products throughout any phase of processing in the tissue establishment shall clearly distinguish released from non-released (quarantined) and rejected products.

4. Records shall demonstrate that before tissues and cells are released all appropriate specifications are met, e.g. all current declaration forms, relevant medical records, processing records and test results have been verified by an authorised person. If a computer is used to release results from the laboratory, an audit trail should indicate who was responsible for their release.

**D. Distribution**

When the activities for which the accreditation / designation / authorisation / licensing is sought include distribution of tissues and cells, the authorised tissue establishment procedures shall comply with the following criteria

1. Critical transport conditions, such as temperature and time limit must be defined to maintain the required tissue and cell properties.

2. The container must ensure that the tissue and cells are maintained in the specified conditions. If the container has not received market validation for this purpose, then relevant critical parameters for the protection of tissue and cell quality shall be defined and maintained in the required range during distribution.

3. 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.

4. A documented system must be in place for the recall of tissue or cells in the event that a potential risk to the recipient(s) is identified following distribution.

5. Procedures shall be in place for the handling of requests for tissues and cells. The considerations and rules for allocation of tissues and cells to certain patients or health care institutions shall be documented and made available to these parties upon request.

6. A documented system must be in place for the handling of returned products including criteria for their acceptance into the inventory, if applicable.

**E. Final labelling for distribution (before distribution)**

1. The primary tissue/cell container shall provide :

   a) Identification number or code of the tissue /cells, and lot or batch number where applicable;

   b) Identification of the tissue establishment

   c) In the case of autologous donation, this has to be specified (for autologous use only) and the donor/recipient has to be identified.

   d) In the case of directed donations - the label shall identify the intended recipient

   e) When a product is known to be positive for a relevant infectious disease marker, or tests results are not available: a BIOLOGICAL HAZARD indicator shall be added.

2. The following information shall be provided either on the label or in accompanying documentation:

   a) Description (definition) and relevant dimensions of the tissue or cell product;

   b) Relevant morphology and functional data;

   c) Date of distribution of the tissue /cells;

   d) Biological determinations carried out on the donor and results;

   e) Storage recommendations and expiry date;

   f) Instructions for opening the container, package, and any required manipulation / reconstitution;

   g) Expiry dates before and after opening /manipulation;

   h) Instructions on reporting serious adverse reactions and /or events.

   i) Presence of potential harmful residues (eg. Antibiotics, ethylene oxide etc)

**F. External labelling of the shipping container**

Every shipping container shall 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 health care establishment of destination, including address and phone number;

c) A statement that the package contains human tissue/cells and HANDLE WITH CARE;

d) In the case of living cells, such as stem cells and gametes, the following shall 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).

## 4. SERIOUS ADVERSE EVENTS AND REACTIONS

1. Member States shall ensure that those facilities where applications of human tissues and cells occur have procedures in place to record the applications, to retain the records for at least 30 years and to notify tissue establishments within 5 working days of any serious adverse event and reactions observed in recipients during or after the application.

2. Member States shall ensure that reporting establishments have procedures in place to communicate to the competent authority within 5 working days all relevant information about suspected serious adverse reactions. Information to be included in the notification is described in Part A of Annex I. The reporting establishment shall analyse the cause and the ensuing outcome and shall submit a report to the competent authority. The information to be included in the report is set out in part B of Annex I

3. Member States shall ensure that reporting establishments have procedures in place to communicate to the competent authority as soon as known, the information as described in part A of Annex II. A report on the analysis of the cause and the ensuing outcome shall be send to the competent authority and conform to part B of Annex II.

4. Member States shall submit to the Commission an annual report, by 30 June of the following year, on the notification of serious adverse reactions and events received by the competent authority.

5. Member States shall ensure that their competent authorities communicate to each other such information as is appropriate with regard to serious adverse reactions and events in order to guarantee that tissues and cells known or suspected to be defective are withdrawn from use and discarded

## 5. TRACEABILITY.

1. Data to be kept to ensure full traceability, as established in Article 8 of Directive 2004/23/EC, are listed below:

a) Donor identification that will include at least:

- Name
- Date of birth
- Sex
- Address (including Country )
- Date of death (if applicable)

b) Donation identification that will include at least:

- Identification of the procurement organisation
- Identification of the Tissue establishment
- Unique Donation ID number
- Date of procurement
- Place of procurement
- Type of donation (e.g. cadaveric, living allogenic, living autologous, tissue engineering, research)

c) Product identification will include at least:

- Identification of the Tissue establishment
- Type of tissue and cell / product (basic Nomenclature)
- Pool number (if applicable)
- Split number (if applicable)
- Expiry date
- Tissue/cell status (i.e. quarantined, suitable for use etc.)
- Identification of the facility issuing the final label

d) Application identification will include at least:

- Date of use/disposal
- Identification of the Clinician or end user / Facility
- Intended use identification
- Country

e) Recipient identification will include at least:

- Identification of the Country number
- Name
- Date of birth
- Sex
- Address

2. To ensure that all human tissues and cells are traceable from donor to recipient or disposal, and vice versa, tissue establishments must:

    a. Have effective, unique and accurate identification and labelling systems for the cells / tissues received and distributed .
    b. Maintain registers of received, processed, stored and distributed or discarded tissues, enabling identification of:
        - individual donors, donations and hospitals or institutions from which tissues and/or cells have been received;
        - processing steps applied to tissues and/or cells and, if applicable, third parties involved in processing;
        - distributed tissues and/or cells and hospitals or institutions to which tissues and/or cells have been distributed (whether intended for application in the human body, research purposes or for manufacturing);

3. Tissue establishments shall have access to an archive of frozen serum samples that includes at least one sample from each allogeneic donor for a minimum period of 2 years after the longest expiry date of the last piece of tissue from the donor, so that tests can be performed if required after any human application.

4. Hospitals and institutions should be able to identify each unit of tissues and/or cells received and the individual patient to which the tissues and cells have been applied.

## 6. EUROPEAN CODING SYSTEM

1. The code assigned to each donation in all tissue establishments must incorporate the following information:

a) Donation identification:

- Unique ID number
- Identification of the Tissue establishment

b) Product identification:

- Product code (basic Nomenclature)
- Split number (if applicable)
- Expiration date

2. Guidelines concerning the specifications, the basic nomenclature and the implementation of the code shall be established by the Commission in collaboration with Member States

## ANNEX I

## NOTIFICATION OF SERIOUS ADVERSE REACTIONS
**Rapid notification for**
**suspected serious adverse reactions**

### PART A

| |
|---|
| **Reporting establishment** |
| **Report identification** |
| **Reporting date (year/month/day)** |
| **Date of application (year/month/day)** |
| **Age and sex of recipient** |
| **Date of serious adverse reaction (year/month/day)** |
| **Serious adverse reaction is related (type of tissue/cells)** |
| **Type of serious adverse reaction(s)** |

### PART B

**Confirmation for**
**serious adverse reactions**

| |
|---|
| **Reporting establishment** |
| **Report identification** |
| **Confirmation date (year/month/day)** |
| **Date of serious adverse reaction (year/month/day)** |
| **Confirmation of serious adverse reaction (Yes / No)** |
| **Change of type of serious adverse reaction (Yes / No)**<br>**If Yes, *Specify*** |
| **Clinical outcome (if known)**<br>– **Complete recovery**<br>– **Minor sequelae**<br>– **Serious sequelae**<br>– **Death** |

## ANNEX II

## NOTIFICATION OF SERIOUS ADVERSE EVENTS
## PART A

### Rapid Notification for
### Serious Adverse Events

| | | | | |
|---|---|---|---|---|
| **Reporting establishment** | | | | |
| **Report identification** | | | | |
| **Reporting date (year/month/day)** | | | | |
| **Date of serious adverse event (year/month/day)** | | | | |
| **Serious adverse event, which may affect quality and safety of tissues and cells due to a deviation in:** | **Specification** | | | |
| | Product defect | Equipment failure | Human error | Other (specify) |
| Procurement | | | | |
| Testing | | | | |
| Transport | | | | |
| Processing | | | | |
| Storage | | | | |
| Distribution | | | | |
| Materials | | | | |
| Others *(specify)* | | | | |

## PART B

### Confirmation for
### Serious Adverse Events

| |
|---|
| **Reporting establishment** |
| **Report identification** |
| **Confirmation date (***year/month/day*) |
| **Date of serious adverse event** *(year/month/day)* |
| **Root cause analysis (details)** |
| **Corrective measures taken (details)** |