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COMMISSION DIRECTIVE 2006/86/EC

of 24 October 2006

implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells

(Text with EEA relevance)

(OJ L 294, 25.10.2006, p. 32)

Amended by:

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**COMMISSION DIRECTIVE 2006/86/EC****of 24 October 2006****implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells****(Text with EEA relevance)**

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells⁽¹⁾, and in particular Article 8, Articles 11(4) and 28(a), (c), (g) and (h) thereof,

Whereas:

- (1) Directive 2004/23/EC lays down standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for human applications, and of manufactured products derived from human tissues and cells intended for human applications, so as to ensure a high level of human health protection.
- (2) In order to prevent the transmission of diseases by human tissues and cells for human applications and to ensure an equivalent level of quality and safety, Directive 2004/23/EC calls for the establishment of specific technical requirements for each one of the steps in the human tissues and cells application process, including standards and specifications with regard to a quality system for tissue establishments.
- (3) An accreditation, designation, authorisation or licensing system for tissue establishments and for the preparation processes at the tissue establishments should be established in Member States in accordance with Directive 2004/23/EC, in order to ensure a high level of protection of human health. It is necessary to lay down the technical requirements for this system.
- (4) The requirements for accreditation, designation, authorisation or licensing of tissue establishments should cover the organisation and management, personnel, equipment and materials, facilities/premises, documentation and records and quality review. Accredited, designated, authorised or licensed tissue establishments should comply with additional requirements for the specific activities they carry out.

⁽¹⁾ OJ L 102, 7.4.2004, p. 48.

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- (5) The air quality standard during the processing of tissues and cells is a key factor that may influence the risk of tissue or cell contamination. An air quality with particle counts and microbial colony counts equivalent to those of Grade A, as defined in the European Guide to Good Manufacturing Practice, Annex 1 and Commission Directive 2003/94/EC ⁽¹⁾, is generally required. However, in certain situations, an air quality with particle counts and microbial colony counts equivalent to those of Grade A standard is not indicated. In these circumstances it should be demonstrated and documented that the chosen environment achieves the quality and safety required for the type of tissue and cells, process and human application concerned.
- (6) The scope of this Directive should embrace the quality and safety of human tissues and cells during coding, processing, preservation, storage and distribution to the healthcare establishment where they will be applied to the human body. However, it should not extend to the human application of these tissues and cells (such as implantation surgery, perfusion, insemination or transfer of embryos). The provisions of this Directive concerning traceability and the reporting of serious adverse reactions and events apply also to the donation, procurement and testing of human tissues and cells regulated by Commission Directive 2006/17/EC ⁽²⁾.
- (7) The use of tissues and cells for human application carries a risk of disease transmission and other potential adverse effects in recipients. In order to monitor and reduce these effects, specific requirements for traceability and a Community procedure for notifying serious adverse reactions and events should be set out.
- (8) Suspected serious adverse reactions, in the donor or in the recipient, and serious adverse events from donation to distribution of tissues and cells, which may influence the quality and safety of tissues and cells and which may be attributed to procurement (including donor evaluation and selection), testing, processing, preservation, storage and distribution of human tissues and cells should be notified without delay to the competent authority.
- (9) Serious adverse reactions may be detected during or following procurement in living donors or during or following human application. They should be reported to the associated tissue establishment for subsequent investigation and notification to the competent authority. This should not preclude a procurement organisation or an organisation responsible for human application from also directly notifying the competent authority if it so wishes. This Directive should define the minimum data needed for notification to the competent authority, without prejudice to the ability of Member States to maintain or introduce in their territory more stringent and protective measures which comply with the requirements of the Treaty.

⁽¹⁾ <http://pharmacos.eudra.org/F2/eudralex/vol-4/home.htm> and OJ L 262, 14.10.2003, p. 22.

⁽²⁾ OJ L 38, 9.2.2006, p. 40.

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- (10) In order to minimise transmission costs, avoid overlaps and increase administrative efficiency, modern technologies and e-government solutions should be used to perform the tasks related to the transmission and treatment of information. These technologies should be based on a standard exchange format using a system suitable for the management of reference data.
- (11) To facilitate traceability and information on the main characteristics and properties of tissues and cells, it is necessary to lay down the basic data to be included in a single European code.
- (12) This Directive respects the fundamental rights and observes the principles recognised in particular by the Charter of Fundamental Rights of the European Union.
- (13) The measures provided for in this Directive are in accordance with the opinion of the Committee set up by Article 29 of Directive 2004/23/EC,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Scope

1. This Directive shall apply to the coding, processing, preservation, storage and distribution of:
 - (a) human tissues and cells intended for human applications; and
 - (b) manufactured products derived from human tissues and cells intended for human applications, where those products are not covered by other directives.
2. The provisions of Articles 5 to 9 of this Directive, concerning traceability and the reporting of serious adverse reactions and events shall also apply to the donation, procurement and testing of human tissues and cells.

Article 2

Definitions

For the purposes of this Directive, the following definitions apply:

- (a) ‘*reproductive cells*’ means all tissues and cells intended to be used for the purpose of assisted reproduction;
- (b) ‘*partner donation*’ means the donation of reproductive cells between a man and a woman who declare that they have an intimate physical relationship;
- (c) ‘*quality system*’ means the organisational structure, defined responsibilities, procedures, processes, and resources for implementing quality management and includes all activities which contribute to quality, directly or indirectly;

▼ B

- (d) ‘*quality management*’ means the coordinated activities to direct and control an organisation with regard to quality;
- (e) ‘*Standard Operating Procedures*’ (*SOPs*) means written instructions describing the steps in a specific process, including the materials and methods to be used and the expected end product;
- (f) ‘*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) ‘*traceability*’ means 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 storing 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;
- (h) ‘*critical*’ means potentially having an effect on the quality and/or safety of or having contact with the cells and tissues;
- (i) ‘*procurement organisation*’ means 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;
- (j) ‘*organisations responsible for human application*’ means a health care establishment or a unit of a hospital or another body which carries out human application of human tissues and cells;

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- (k) ‘*Single European Code*’ or ‘*SEC*’ means the unique identifier applied to tissues and cells distributed in the Union. The Single European Code consists of a donation identification sequence and a product identification sequence, as further specified in Annex VII to this Directive;
- (l) ‘*donation identification sequence*’ means the first part of the Single European Code consisting of the EU tissue establishment code and the unique donation number;
- (m) ‘*EU tissue establishment code*’ means the unique identifier for accredited, designated, authorised, or licensed tissue establishments in the Union. The tissue establishment code consists of an ISO country code and the tissue establishment number set out in the EU Tissue Establishment Compendium, as further specified in Annex VII to this Directive;

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- (n) ‘*unique donation number*’ means the unique number attributed to a specific donation of tissues and cells in line with the system in place in each Member State for allocating such numbers, as further specified in Annex VII to this Directive;
- (o) ‘*product identification sequence*’ means the second part of the Single European Code consisting of the product code, the split number and the expiry date;
- (p) ‘*product code*’ means the identifier for the specific type of tissue and cell in question. The product code consists of the product coding system identifier indicating the coding system used by the tissue establishment (‘E’ for the EUTC, ‘A’ for ISBT128, ‘B’ for Eurocode) and the tissues and cells product number foreseen in the respective coding system for the product type, as further defined in Annex VII to this Directive;
- (q) ‘*split number*’ means the number which distinguishes and uniquely identifies tissues and cells having the same unique donation number and the same product code and originating from the same tissue establishment, as further defined in Annex VII to this Directive;
- (r) ‘*expiry date*’ means the date by which the tissues and cells can be applied, as further defined in Annex VII to this Directive;
- (s) ‘*EU Coding Platform*’ means the IT platform hosted by the Commission which contains the EU Tissue Establishment Compendium and the EU Tissue and Cell Product Compendium;
- (t) ‘*EU Tissue Establishment Compendium*’ means the register of all tissue establishments which are authorised, licensed, designated or accredited by the Member States’ competent authority or authorities and which contains the information about these tissue establishments as set out in Annex VIII to this Directive;
- (u) ‘*EU Tissue and Cell Product Compendium*’ means the register of all types of tissues and cells circulating in the Union and the respective product codes under the three permitted coding systems (EUTC, ISBT128 and Eurocode);
- (v) ‘*EUTC*’ means the product coding system for tissues and cells developed by the Union consisting of a register of all types of tissues and cells circulating in the Union and their corresponding product codes;
- (w) ‘*released for circulation*’ means distribution for human application or transfer to another operator, e.g. for further processing with or without return;

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- (x) ‘*within the same centre*’ means that all steps from procurement to human application are carried out under the same responsible person, quality management system and traceability system, within a healthcare centre comprising at least an accredited, designated, authorised, or licensed tissue establishment and an organisation responsible for human application at the same location;
- (y) ‘*pooling*’ means the physical contact or mixing in a single container, of tissues or cells from more than one procurement from the same donor, or from two or more donors.

▼ B*Article 3***Requirements for the accreditation, designation, authorisation or licensing of tissue establishments**

A tissue establishment must comply with the requirements set out in Annex I.

*Article 4***Requirements for the accreditation, designation, authorisation, licensing of tissue and cell preparation processes**

Preparation processes at the tissue establishments must comply with the requirements set out in Annex II.

*Article 5***Notification of serious adverse reactions**

1. Member States shall ensure that:
 - (a) procurement organisations have procedures in place to retain the records of tissues and cells procured and to notify tissue establishments without delay of any serious adverse reactions in the living donor which may influence the quality and safety of tissues and cells;
 - (b) organisations responsible for human application of tissues and cells have procedures in place to retain the records of tissues and cells applied and to notify tissue establishments without delay of any serious adverse reactions observed during and after clinical application which may be linked to the quality and safety of tissues and cells;
 - (c) tissue establishments that distribute tissue and cells for human application provide information to the organisation responsible for human application of tissues and cells about how that organisation should report serious adverse reactions as referred to in (b).
2. Member States shall ensure that tissue establishments:
 - (a) have procedures in place to communicate to the competent authority without delay all relevant available information about suspected serious adverse reactions as referred to in paragraph 1(a) and (b);

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- (b) have procedures in place to communicate to the competent authority without delay the conclusion of the investigation to analyse the cause and the ensuing outcome.
3. Member States shall ensure that:
- (a) the responsible person referred to in Article 17 of Directive 2004/23/EC notifies the competent authority of the information included in the notification set out in Part A of Annex III;
 - (b) tissue establishments notify the competent authority of the actions taken with respect to other implicated tissues and cells that have been distributed for human applications;
 - (c) tissue establishments notify the competent authority of the conclusion of the investigation, supplying at least the information set out in Part B of Annex III.

*Article 6***Notification of serious adverse events**

1. Member States shall ensure that:
- (a) procurement organisations and tissue establishments have procedures in place to retain the records and to notify tissue establishments without delay of any serious adverse events that occur during procurement which may influence the quality and/or safety of human tissues and cells;
 - (b) organisations responsible for human application of tissues and cells have procedures in place to notify tissue establishments without delay of any serious adverse events that may influence the quality and safety of the tissues and cells;
 - (c) tissue establishments provide to the organisation responsible for human application information about how that organisation should report serious adverse events to them that may influence the quality and safety of the tissues and cells.
2. In the case of assisted reproduction, any type of gamete or embryo misidentification or mix-up shall be considered to be a serious adverse event. All persons or procurement organisations or organisations responsible for human application performing assisted reproduction shall report such events to the supplying tissue establishments for investigation and notification to the competent authority.
3. Member States shall ensure that tissue establishments:
- (a) have procedures in place to communicate to the competent authority without delay all relevant available information about suspected serious adverse events as referred to in paragraph 1(a) and (b);
 - (b) have procedures in place to communicate to the competent authority without delay the conclusion of the investigation to analyse the cause and the ensuing outcome.

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4. Member States shall ensure that:
- (a) the responsible person referred to in Article 17 of Directive 2004/23/EC notifies the competent authority of the information included in the notification set out in Part A of Annex IV;
 - (b) tissue establishments evaluate serious adverse events to identify preventable causes within the process;
 - (c) tissue establishments notify the competent authority of the conclusion of the investigation, supplying at least the information set out in Part B of Annex IV.

*Article 7***Annual reports**

1. 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. The Commission shall submit to the competent authorities of Member States a summary of the reports received. The competent authority shall make this report available to tissue establishments.

2. Data transmission shall comply with the data exchange format specifications as set out in Annex V, part A and B, and shall provide all the information necessary to identify the sender and maintain its reference data.

*Article 8***Communication of information between competent authorities and to the Commission**

Member States shall ensure that their competent authorities communicate to each other and to the Commission such information as is appropriate with regard to serious adverse reactions and events, in order to guarantee that adequate actions are taken.

▼M1*Article 9***Traceability**

1. Member States shall ensure that tissues and cells shall be traceable in particular through documentation and the use of the Single European Code from procurement to human application or disposal and vice versa. Tissues and cells used for advanced therapy medicinal products shall be traceable under this Directive at least until transferred to the ATMP manufacturer.

2. Member States shall ensure that tissue establishments and organisations responsible for human application shall retain the data set out in Annex VI for at least 30 years, using an appropriate and readable storage medium.

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3. In case of tissues and cells retrieved from a deceased donor by procurement teams operating for two or more tissue establishments, Member States shall ensure an appropriate traceability system across the procurements.

*Article 10***European coding system**

1. Without prejudice to paragraphs 2 or 3 of this Article, a Single European Code shall be applied to all tissues and cells distributed for human application. For the other situations where tissues and cells are released for circulation, as a minimum the donation identification sequence shall be applied at least in the accompanying documentation.

2. Paragraph 1 shall not apply to:

- (a) reproductive cells from partner donation;
- (b) tissues and cells distributed directly for immediate transplantation to the recipient, as referred to in Article 6(5) of Directive 2004/23/EC;
- (c) tissues and cells imported into the Union in case of emergency authorised directly by the competent authority or authorities, as referred to in Article 9(3)b of Directive 2004/23/EC.

3. Member States may also allow exemptions from the requirement provided for in paragraph 1 for:

- (a) tissues and cells other than reproductive cells for partner donation, when these tissues and cells remain within the same centre;
- (b) tissues and cells that are imported into the Union, when these tissues and cells remain within the same centre from importation to application, provided that the centre comprises a tissue establishment authorised, designated, accredited, or licensed to carry out importing activities.

*Article 10a***Format of the Single European Code**

1. The Single European Code referred to in Article 10(1) shall comply with the specifications set out in this Article and in Annex VII.

2. The Single European Code shall be in eye-readable format and shall be preceded by the acronym 'SEC'. The parallel use of other labelling and traceability systems is possible.

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3. The Single European Code shall be printed with the Donation Identification Sequence and Product Identification Sequence separated by a single space or as two successive lines.

*Article 10b***Requirements related to the application of the Single European Code**

1. Member States shall ensure that the following minimum requirements are complied with by tissue establishments, including importing tissue establishments as defined by Commission Directive (EU) 2015/566 ⁽¹⁾:

- (a) allocate a Single European Code to all tissues and cells requiring application of this code at the latest before their distribution for human application;
- (b) allocate a donation identification sequence after procuring the tissues and cells, or when receiving them from a procurement organisation, or when importing tissues and cells from a third country supplier. The donation identification sequence shall include:
 - (1) their EU tissue establishment code as assigned in the EU Tissue Establishment Compendium;
 - (2) a unique donation number allocated by the tissue establishment, unless such number is allocated centrally at national level or is a globally unique number as used by the ISBT128 coding system. Where allowed, in case of pooling of tissues and cells, a new donation identification number shall be allocated to the final product; traceability with the individual donations shall be ensured by the tissue establishment in which pooling is carried out;
- (c) do not alter the donation identification sequence once it is allocated to tissues and cells released for circulation, unless it is necessary to correct an encoding error; any correction requires proper documentation;
- (d) use one of the permitted product coding systems and the corresponding tissue and cell product numbers included in the EU Tissue and Cell Product Compendium at the latest before their distribution for human application;
- (e) use an appropriate split number and expiry date. For tissues and cells for which no expiry date is defined, the expiry date shall be 00000000 at the latest before their distribution for human application;

⁽¹⁾ Commission Directive (EU) 2015/566 of 8 April 2015 implementing Directive 2004/23/EC as regards the procedures for verifying the equivalent standards of quality and safety of imported tissue (OJ L 93, 9.4.2015, p. 56).

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- (f) apply the Single European Code on the label of the product concerned in an indelible and permanent manner and mention that code in the relevant accompanying documentation at the latest before its distribution for human application. The tissue establishment may entrust this task to a third party or third parties, provided the tissue establishment ensures compliance with this Directive, in particular in terms of uniqueness of the code. Where the label size precludes the application of the Single European Code on the label, the code shall be unambiguously linked to tissues and cells packaged with such a label through the accompanying documentation;
 - (g) notify the competent authority or authorities when:
 - (1) information contained in the EU Tissue Establishment Compendium requires an update or correction;
 - (2) the EU Tissue and Cell Product Compendium requires an update;
 - (3) the tissue establishment observes a situation of significant non-compliance with the requirements relating to the Single European Code concerning tissues and cells received from other EU tissue establishments;
 - (h) take the necessary measures in case of incorrect application of the Single European Code on the label.
2. Member States shall ensure that the following minimum requirements are applied by all competent authorities:
- (a) ensure the allocation of a unique tissue establishment number to all tissue establishments authorised, accredited, designated or licensed in its Member State. If a tissue establishment has different physical locations, but has one system for allocating unique donation numbers, it may be deemed to be one and the same tissue establishment. If a tissue establishment uses two or more systems to allocate unique donation numbers, such an entity shall be allocated separate tissue establishment numbers corresponding to the number of allocation systems used;
 - (b) decide which system or systems shall be used for the allocation of unique donation numbers in their Member State. Permitted systems of allocation include national systems establishing centralised allocation of the nationally unique donation number or systems requiring each tissue establishment to allocate unique donation numbers or international systems that allocate globally unique donation numbers that are compatible with the Single European Code.
 - (c) monitor and enforce the full implementation of the Single European Code in their Member State;
 - (d) ensure the validation of the data on the tissue establishments contained in the EU Tissue Establishment Compendium for their Member State and update the Compendium without undue delay in particular in the following situations:

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- (1) when a new tissue establishment is authorised, designated, accredited, or licensed;
- (2) when tissue establishment information changes or is not correctly recorded in the EU Tissue Establishment Compendium;
- (3) when the accreditation, designation, authorisation or licence details of a tissue establishment, as listed in Annex VIII to this Directive, change, including:
 - accreditation, designation, authorisation or licence for a new tissue or cell type,
 - accreditation, designation, authorisation or licence for a new prescribed activity,
 - details of any conditions and or exemptions added to an authorisation,
 - suspension, in part or in full, of a specific accreditation, designation, authorisation or licence for a particular activity or tissue or cell type;
 - revocation, in part or in full, of an accreditation, designation, authorisation or licence for a tissue establishment,
 - situations when a tissue establishment voluntarily ceases, in part or in full, the activity or activities for which it is authorised, accredited, designated or licensed.

Without undue delay means in not later than 10 working days for any changes substantially affecting the authorisation, accreditation, designation or licence of the tissue establishments concerned.

When a tissue establishment is authorised by two or more competent authorities for different types of tissues and cells or different activities, each competent authority shall update the information relating to those activities for which it is responsible;

- (e) Alert the competent authorities of another Member State when they observe incorrect information in the EU Tissue Establishment Compendium relating to the other Member State or when they observe a situation of significant non-compliance with the provisions relating to the Single European Code relating to the other Member State;
- (f) Alert the Commission and the other Competent Authorities when in their assessment the EU Tissue and Cell Product Compendium requires an update.

3. The application of the Single European Code does not preclude the additional application of other codes in accordance with Member States' national requirements.

▼M1*Article 10c***Accessibility and maintenance of the European coding system**

1. The Commission shall host and maintain an IT platform ('EU Coding Platform') which contains:

- (a) the EU Tissue Establishment Compendium;
- (b) the EU Tissue and Cell Product Compendium.

2. The Commission shall ensure that the information contained in the EU Coding Platform is publicly available before 29 October 2016.

3. The Commission shall update when needed the EUTC and ensure the overall update of the EU Tissue and Cell Product Compendium. The Commission considers that it is necessary that agreements are established with the organisations managing ISBT128 and Eurocode to ensure that updated product codes are regularly made available to the Commission for inclusion in the EU Tissue and Cell Product Compendium. If such organisations do not comply with the terms of the memoranda of understanding, the Commission may suspend, partially or in full, the future use of their respective product codes, having considered the sufficient supply of the concerned type of products in the Member States including a transitional period and having consulted the Member State experts through the Competent Authorities on Substances of Human Origin Expert Group.

*Article 10d***Transitional period**

Tissues and cells already in storage on 29 October 2016 shall be exempted from the obligations relating to the Single European Code, provided the tissues and cells are released for circulation in the Union within five years following that date and under the condition that full traceability is ensured by alternative means. For tissues and cells which remain in storage and which are only released for circulation after the expiry of this five-year period and for which the application of the Single European Code is not possible, in particular because the tissues and cells are stored under deep-freeze conditions, the tissue establishments shall use the procedures applicable to products with small labels as laid down in Article 10b paragraph 1(f).

▼B*Article 11***Transposition**

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 1 September 2007, at the latest. They shall forthwith communicate to the Commission the text of those provisions and a correlation table between those provisions and this Directive.

Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with Article 10 of this Directive, by 1 September 2008.

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When Member States adopt those provisions, they shall contain a reference to this Directive or be accompanied by such a reference on the occasion of their official publication. Member States shall determine how such reference is to be made.

2. Member States shall communicate to the Commission the text of the main provisions of national law which they adopt in the field covered by this Directive.

*Article 12***Entry into force**

This Directive shall enter into force on the 20th day following its publication in the *Official Journal of the European Union*.

*Article 13***Addressees**

This Directive is addressed to the Member States.

*ANNEX I***Requirements for accreditation, designation, authorisation or licensing of tissue establishments as referred to in Article 3****A. ORGANISATION AND MANAGEMENT**

1. A responsible person must be appointed having qualifications and responsibilities as provided 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 must be an organisational chart which clearly defines accountability and reporting relationships.
3. Every tissue establishment must have access to a nominated medical registered practitioner to advise on and oversee the establishment's medical activities such as donor selection, review of clinical outcomes of applied tissues and cells or interaction as appropriate with clinical users.
4. 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.
5. 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 in particular to the procedures, environment, staff health status specific to the tissue establishment.
6. Agreements between tissue establishments and third parties must comply with Article 24 of Directive 2004/23/EC. Third party agreements must specify the terms of the relationship and responsibilities as well as the protocols to be followed to meet the required performance specification.
7. 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.
8. In the event of termination of activities the agreements concluded and the procedures adopted in accordance with Article 21(5) of Directive 2004/23/EC shall include traceability data and material concerning the quality and safety of cells and tissues.
9. There must be a documented system in place that ensures the identification of every unit of tissue or cells at all stages of the activities for which accreditation/designation/authorisation/licensing is sought.

B. PERSONNEL

1. 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.
2. All personnel should have clear, documented and up-to-date job descriptions. Their tasks, responsibilities and accountability must be clearly documented and understood.

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3. 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;
 - (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.

C. EQUIPMENT AND MATERIALS

1. All equipment and material must be designed and maintained to suit its intended purpose and must minimise any hazard to recipients and/or staff.
2. All critical equipment and technical devices must be identified and validated, regularly inspected and preventively maintained in accordance with the manufacturers' instructions. Where equipment or materials affect critical processing or storage parameters (e.g. temperature, pressure, particle counts, microbial contamination levels), they must be identified and must be the subject of appropriate monitoring, alerts, alarms and corrective action, as required, to detect malfunctions and defects and to ensure that the critical parameters are maintained within acceptable limits at all times. All equipment with a critical measuring function must be calibrated against a traceable standard if available.
3. New and repaired equipment must be tested when installed and must be validated before use. Test results must be documented.
4. Maintenance, servicing, cleaning, disinfection and sanitation of all critical equipment must 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, must be available.
6. The procedures for the activities for which accreditation/designation/authorisation/licensing is sought, must detail the specifications for all critical materials and reagents. In particular, specifications for additives (e.g. solutions) and packaging materials must be defined. Critical reagents and materials must meet documented requirements and specifications and when applicable the requirements of Council Directive 93/42/EEC of 14 June 1993 concerning medical devices⁽¹⁾ and Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices⁽²⁾.

⁽¹⁾ OJ L 169, 12.7.1993, p. 1. Directive as last amended by Regulation (EC) No 1882/2003 of the European Parliament and of the Council (OJ L 284, 31.10.2003, p. 1).

⁽²⁾ OJ L 331, 7.12.1998, p. 1. Directive as amended by Regulation (EC) No 1882/2003.



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 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 point 4, 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 current European Guide to Good Manufacturing Practice (GMP), Annex 1 and Directive 2003/94/EC is required with a background environment appropriate for the processing of the tissue/cell concerned but at least equivalent to GMP Grade D in terms of particles and microbial counts.
4. A less stringent environment than specified in point 3 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).
5. In point 4(a), (b), (c) and (d), 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.
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, humidity or air quality must be defined.

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7. Critical parameters (e.g. temperature, humidity, air quality) must be controlled, monitored, and recorded to demonstrate compliance with the specified storage conditions.
8. 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.
9. 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.

E. DOCUMENTATION AND RECORDS

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 Directive. 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 tissue establishments 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.
7. Without prejudice to Article 9(2), 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 at least 10 years after expiry date, clinical use or disposal.
8. Records must meet the confidentiality requirements laid down in Article 14 of Directive 2004/23/EC. 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.

▼B**F. QUALITY REVIEW**

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.
2. 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.
3. 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.
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.

*ANNEX II***Requirements for the authorisation of tissue and cell preparation processes at the tissue establishments as referred to in Article 4**

The competent authority shall authorise each tissue and cell preparation process after evaluation of the donor selection criteria and procurement procedures, the protocols for each step of the process, the quality management criteria, and the final quantitative and qualitative criteria for cells and tissues. This evaluation must comply at least with the requirements set out in this Annex.

A. RECEPTION AT THE TISSUE ESTABLISHMENT

Upon reception of procured tissues and cells at the tissue establishment, the tissues and cells must comply with the requirements defined in Directive 2006/17/EC.

B. PROCESSING

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

1. The critical processing procedures must be validated and must not render the tissues or cells clinically ineffective or harmful to the recipient. This validation may be based on studies performed by the establishment itself, or on data from published studies or, for well established processing procedures, by retrospective evaluation of the clinical results for tissues supplied by the establishment.
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.
3. The procedures must be documented in SOPs which must conform to the validated method and to the standards laid down in this Directive, accordingly with Annex I(E), points 1 to 4.
4. It must be ensured that all processes are conducted in accordance with the approved SOPs.
5. Where a microbial inactivation procedure is applied to the tissue or cells, it must be specified, documented, and validated.
6. Before implementing any significant change in processing, the modified process must be validated and documented.
7. The processing procedures must undergo regular critical evaluation to ensure that they continue to achieve the intended results.
8. Procedures for discarding tissue and cells must prevent the contamination of other donations and products, the processing environment or personnel. These procedures must comply with national 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 must comply with the following criteria:

1. Maximum storage time must be specified for each type of storage condition. The selected period must reflect among others possible deterioration of the required tissue and cell properties.

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2. 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.
3. 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.
4. 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 as specified in Article 17 of Directive 2004/23/EC. If a computer is used to release results from the laboratory, an audit trail should indicate who was responsible for their release.
5. A documented risk assessment approved by the responsible person as defined in Article 17 of Directive 2004/23/EC 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.

D. DISTRIBUTION AND RECALL

When the activities for which the accreditation/designation/authorisation/licensing is sought include distribution of tissues and cells, the authorised tissue establishment procedures must 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/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.
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. There must be personnel authorised within the tissue establishment to assess the need for recall and to initiate and coordinate the necessary actions.
5. 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.
6. Actions must be taken within pre-defined periods of time and must include tracing all relevant tissues and cells and, where applicable, must include trace-back. The purpose of the investigation is to identify any donor who might have contributed to causing the reaction in the recipient and to retrieve available tissues and cells from that donor, as well as to notify consignees and recipients of tissues and cells procured from the same donor in the event that they might have been put at risk.

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7. Procedures must be in place for the handling of requests for tissues and cells. The rules for allocation of tissues and cells to certain patients or health care institutions must be documented and made available to these parties upon request.
8. 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

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;

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- (g) Single European Code as applicable to the tissues and cells being distributed for human application or the donation identification sequence as applicable to the tissues and cells released for circulation, other than distributed for human application.

If any of the information under points (d), (e) and (g) 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.

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2. 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 Articles 5 to 6;
 - (i) presence of potential harmful residues (e.g. antibiotics, ethylene oxide etc);

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- (j) for imported tissues and cells, the country of procurement and the exporting country (if different from the procurement country).

▼B**F. EXTERNAL LABELLING OF THE SHIPPING CONTAINER**

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).

▼ **M1***ANNEX III***NOTIFICATION OF SERIOUS ADVERSE REACTIONS**

PART A

Rapid notification for suspected serious adverse reactions

Tissue establishment
EU tissue establishment code (if applicable)
Report identification
Reporting date (year/month/day)
Individual affected (recipient or donor)
Date and place of procurement or human application (year/month/day)
Unique donation identification number
Date of suspected serious adverse reaction (year/month/day)
Type of tissues and cells involved in the suspected serious adverse reaction
Single European Code of tissues or cells involved in the suspected serious adverse reaction (if applicable)
Type of suspected serious adverse reaction(s)

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PART B

Conclusions of Serious Adverse Reactions Investigation

Tissue establishment
EU tissue establishment code (if applicable)
Report identification
Confirmation date (year/month/day)
Date of serious adverse reaction (year/month/day)
Unique donation identification number
Confirmation of serious adverse reaction (Yes/No)
Single European Code of tissues or cells involved in the confirmed serious adverse reaction (if applicable)
Change of type of serious adverse reaction (Yes/No) If YES, specify
Clinical outcome (if known) — Complete recovery — Minor sequelae — Serious sequelae — Death
Outcome of the investigation and final conclusions
Recommendations for preventive and corrective actions

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ANNEX IV

NOTIFICATION OF SERIOUS ADVERSE EVENTS

PART A

Rapid notification for suspected serious adverse events

Tissue establishment				
EU tissue establishment code (if applicable)				
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			
	Tissues and cells defect	Equipment failure	Human error	Other (specify)
Procurement				
Testing				
Transport				
Processing				
Storage				
Distribution				
Materials				
Others (specify)				

PART B

Conclusions of Serious Adverse Events investigation

Tissue establishment
EU tissue establishment code (if applicable)
Report identification
Confirmation date (year/month/day)
Date of serious adverse event (year/month/day)
Root cause analysis (details)
Corrective measures taken (details)



ANNEX V

ANNUAL NOTIFICATION FORMAT

PART A

Annual notification format for serious adverse reactions

Reporting country			
Reporting date 1 January-31 December (year)			
Number of serious adverse reaction(s) per type of tissue and cell (or product in contact with the tissues and cells)			
	Type of tissue/cell (or product in contact with the tissues and cells)	Number of serious adverse reaction(s)	Total number of tissues/cells of this type distributed (if available)
1			
2			
3			
4			
...			
Total			
Total number of tissues and cells distributed (including type of tissue and cell for which no serious adverse reactions were reported):			
Number of recipients affected (total number of recipients):			
Nature of the serious adverse reactions reported		Total number of serious adverse reaction(s)	
Transmitted bacterial infection			
Transmitted viral infection	HBV		
	HCV		
	HIV-1/2		
	Other (Specify)		
Transmitted parasitical infection	Malaria		
	Other (Specify)		
Transmitted malignant diseases			
Other disease transmissions			
Other serious reactions (Specify)			

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PART B

Annual notification format for serious adverse events

Reporting country				
Reporting date 1 January-31 December (<i>year</i>)				
Total number of tissues and cells processed				
Total number of serious adverse events, which may have affected quality and safety of tissues and cells due to a deviation in:	Specification			
	Tissues and cells defect (<i>specify</i>)	Equipment failure (<i>specify</i>)	Human error (<i>specify</i>)	Other (<i>specify</i>)
Procurement				
Testing				
Transport				
Processing				
Storage				
Distribution				
Materials				
Others (<i>specify</i>)				

▼ M1*ANNEX VI***Minimum data to be kept in accordance with Article 9(2)****A. BY TISSUE ESTABLISHMENTS**

- (1) Donor identification
- (2) Donation identification that will include at least:
 - Identification of the procurement organisation (including contact details) or the tissue establishment
 - Unique donation number
 - Date of procurement
 - Place of procurement
 - Type of donation (e.g. single v multi-tissue; autologous v allogenic; living v deceased)
- (3) Product identification that will include at least:
 - Identification of the tissue establishment
 - Type of tissue and cell/product (basic nomenclature)
 - Pool number (in case of pooling)
 - Split number (if applicable)
 - Expiry date (if applicable)
 - Tissue/cell status (i.e. quarantined, suitable for use, etc.)
 - Description and origin of the products, processing steps applied, materials and additives coming into contact with tissues and cells and having an effect on their quality and/or safety.
 - Identification of the facility issuing the final label
- (4) Single European Code (if applicable)
- (5) Human application identification that will include at least:
 - Date of distribution/disposal
 - Identification of the clinician or end-user/facility

B. BY ORGANISATIONS RESPONSIBLE FOR HUMAN APPLICATION

- (1) Identification of the supplier tissue establishment
- (2) Identification of the clinician or end-user/facility
- (3) Type of tissues and cells
- (4) Product identification
- (5) Identification of the recipient
- (6) Date of application
- (7) Single European Code (if applicable)

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ANNEX VII

THE STRUCTURE OF THE SINGLE EUROPEAN CODE

DONATION IDENTIFICATION SEQUENCE			PRODUCT IDENTIFICATION SEQUENCE			
EU TISSUE ESTABLISHMENT CODE		UNIQUE DONATION NUMBER	PRODUCT CODE		SPLIT NUMBER	EXPIRY DATE (YYYYMMDD)
ISO country code	Tissue establishment number		Product Coding System identifier	Product number		
2 alphabetic characters	6 alphanumeric characters	13 alphanumeric characters	1 alphabetic character	7 alphanumeric characters	3 alphanumeric characters	8 numeric characters

▼ M1*ANNEX VIII***Data to be recorded in the EU Tissue Establishment Compendium**

- A. Tissue establishment information
 - 1. Name of the tissue establishment
 - 2. National or international code of tissue establishment
 - 3. Name of the organisation in which the tissue establishment is located (if applicable)
 - 4. Address of the tissue establishment
 - 5. Publishable contact details: functional e-mail address, phone and fax
- B. Details on the authorisation, accreditation, designation, or license of the tissue establishment
 - 1. Name of the authorising, accrediting, designating or licensing competent authority or authorities
 - 2. Name of the national competent authority or authorities responsible for maintenance of the EU Tissue Establishment Compendium
 - 3. Name of the authorisation, accreditation, designation or licence holder (if applicable)
 - 4. Tissues and cells for which the authorisation, accreditation, designation or license was granted
 - 5. Activities actually carried out for which the authorisation, accreditation, designation or licence was granted
 - 6. Status of the authorisation, accreditation, designation or license (authorised, suspended, revoked, in part or in full, voluntary cessation of activities)
 - 7. Details of any conditions and exemptions added to the authorisation (if applicable).