Draft

COMMISSION DIRECTIVE ../…/EC

of

implementing Directive 2004/23/EC of the European Parliament and of the Council as regards 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, and in particular Article 152(4)(a) thereof,

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 points (a), (c), (g) and (h) of Article 28 thereof,

Whereas:

(1) Directive 2004/23/EC lays down standards of quality and safety for the processing, preservation, storage and distribution of all human tissues and cells intended for human applications, and of manufactured products derived from human tissues and cells intended for human applications in they are not covered by other Directives, 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 process of human application, including standards and specifications with regard to a quality system for tissue establishments.

(3) An accreditation, designation, authorisation or licensing system for tissue establishment and for the preparation processes at the tissue establishments should be established in Member States in accordance with Directive 2004/23/EC. This Directive lays down the technical requirements to be applied for these accreditations.

(4) The accreditation of Tissue establishments should include the organisation and management, personnel, equipment and materials, facilities/premises, documentation and registry and quality review. In addition accredited, designated, authorised or

[1] OJ L 102, 7.4.2004, p. 48.

licensed Tissue establishments should comply with additional requirements for the specific activities they carry out.

(5) The air quality standard that is achieved during the processing of tissues and cells is a key factor that may influence the risk of tissue or cell contamination. This Directive refers to the definitions laid down in the European Guide to Good Manufacturing Practice, Annex 1 of Commission Directive 2003/94/EC, and a Grade A standard, as defined in that Directive, is generally required here. However, it is recognised that this Directive regulates a wide range of human tissues and cells with widely varying risks of bacterial/fungal transmission, depending on the processes applied during preparation and on the mode of application of the tissues or cells to the recipient. In a number of these situations, this high air quality standard is not indicated. In these circumstances, where A grade is not indicated, it has to 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.

(6) This Directive regulates the quality and safety of human tissues and cells during processing, preservation, storage and distribution to the healthcare establishment where they will be applied to the human body. However its scope does not extend to the human application of these tissues and cells (e.g. implantation surgery, perfusion, insemination or transfer of embryos).

(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 Directive 2004/23/EC calls for the establishment of specific requirements for traceability and a community procedure for notifying serious adverse reactions and events.

(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 be attributable to the quality and/or safety of procurement, testing, processing, preservation, storage and distribution of human tissues and cells should be notified to the Competent Authority as soon as known. Serious adverse reactions will be detected during or following procurement in living donors or during or following human application. These must be reported to the associated tissue establishment for subsequent investigation and notification to the Competent Authority; this does not preclude a procurement organisation or a clinical unit from also directly notifying the Competent Authority if they so wish. The Directive defines the minimum data needed for notification to the Competent Authority, without prejudice to the faculty of Member States to maintain or introduce in their territory more stringent and protective measures which comply with the requirements of the Treaty as provided under Article 4.2 of Directive 2004/23/EC.

(9) In order to minimise transmission costs, avoid overlaps and increase administrative efficiency, it is strongly encouraged to use modern technologies and e-government solutions to perform the tasks related to the transmission and treatment of information foreseen in Directive 2004/23/EC. These technologies should be based on a standard exchange format using a system suitable for the management of reference data.

(10) Directive 2004/23/EC calls for the establishment of a system for the identification of human tissues and cells in order to facilitate traceability and calls for the design of a

single European coding system to provide information on the main characteristics and properties of tissues and cells. This Directive lays down the basic information for inclusion in this code in order to achieve the proposed objectives. Further guidelines concerning the specifications, the basic nomenclature and the implementation of the code should be established by the Commission in collaboration with Member States

(11) This Directive is based on international experience drawn upon through an extensive consultation and by reference to the Council of Europe's Guide to safety and quality assurance for organs, tissues and cells. The Directive is consistent with the fundamental principles set out in the European Charter of Fundamental Rights.

(12) The measures provided for in this Directive are in accordance with the opinion of the Committee set up by Directive 2004/23/EC,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Scope

This Directive shall apply to the coding, processing, preservation, storage and distribution of all human tissues and cells intended for human applications, and of manufactured products derived from human tissues and cells intended for human applications in they are not covered by other Directives, so as to ensure a high level of human health protection

For the direct use of reproductive cells from partner donation Articles 3, 4, 9 and 10 of this Directive do not apply.

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) *'direct use'* means any procedure where cells are donated and used without any banking;

(d) *'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;

(e) *´quality management`* means the co-ordinated activities to direct and control an organisation with regard to quality.

(f) '*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;

(g) *'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;

(h) *'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;

(i) *´Critical`* means potentially having an effect on the quality and/or safety or having contact with the cells and tissues

(j) *'serious adverse event'* means any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity;

(k) '*serious adverse reaction*' means an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity.

Article 3

Requirements for the accreditation, designation, authorisation or licensing of Tissues establishments

1. Member States shall ensure that the processing, preservation, storage and distribution of Tissues and cells is undertaken by accredited, designated, authorised or licensed tissue establishments according with Article 6 of Directive 2004/23/EC.

2. The Competent authority or authorities shall verify that the tissue establishments comply with the requirements set out in Annex I for their accreditation, designation, authorisation or licensing

Article 4

Criteria for accreditation, designation, authorisation, licensing of tissue and cell preparation processes at the tissue establishments

1. The Competent authority or authorities shall accredit, designate, authorise or license the tissue and cell preparation processes carried out by the Tissue establishment.

2. In addition to meeting the general requirements for accreditation, designation, authorisation or licensing referred to in Article 1 section 2 above, tissue establishments shall comply with the criteria for the specific activities they carry out, set out in Annex II.

Article 5

Notification of serious adverse reactions

1. Member States shall ensure that those organisations responsible for procurement or human application of tissues and cells have procedures in place to retain the records of tissues and cells procured or applied and to notify tissue establishments without delay of any serious adverse reactions observed which may be attributable to the quality and/or safety of procurement, testing, processing, preservation, storage and distribution of human tissues and cells, as well as any serious adverse reaction observed during or after the clinical application which may be linked to the quality and/or safety of the tissues and cells applied .[PL suggests to incorporate a new annex: Information to be included in the notification from the organisations responsible for procurement or human application of tissues and cells to the Tissue establishment]

2. Member States shall ensure that tissue establishments have procedures in place to communicate to the competent authority as soon as known all relevant available information about suspected serious adverse reactions. Information to be included in the notification is described in Part A of Annex III. The tissue establishment shall analyse the cause and the ensuing outcome. 3. Member States shall ensure that tissue establishments:

(a) notify the competent authority of any case of transmission of infectious agents by tissues and cells or of any other suspected serious adverse reaction in a recipient or a living donor which may be attributable to the quality and/or safety of procurement, testing, processing, preservation, storage and distribution of human tissues or cells as soon as known;

(b) describe the actions taken with respect to other implicated tissues and cells that have been distributed for human applications;

(c) complete the serious adverse reaction notification, upon conclusion of the investigation, including at least the information set out in Part B of Annex III

(d) that distribute tissue and cells for human application provide to the receiving centre information about how the receiving centre should report serious adverse reactions to them that are attributable to the quality and properties of the tissues and cells.;

Article 6

Notification of serious adverse events

1. Member States shall ensure that procurement organisations and tissue establishments have procedures in place to retain the record of any serious adverse events which may be attributable to the quality and/or safety of procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

2. Procurement organisations shall report to the associated tissue establishments any serious adverse events that occur during procurement.

3. 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 establishments performing these clinical procedures shall report such events to the supplying tissue establishments for investigation and notification to the Competent Authority

4. Member States shall ensure that tissue establishments have procedures in place to communicate to the competent authority as soon as known, the information as described in part A of Annex IV.

5 Member States shall ensure that tissue establishments:

(a) evaluate serious adverse events to identify preventable causes within the process;

(b) complete the serious adverse event notification, upon conclusion of the investigation, using at least the information set out in Part B of Annex IV;

(c) that distribute tissue and cells for human application provide to the receiving centre information about how the receiving centre should report serious adverse events to them that are attributable to the quality and properties of the tissues and cells.;

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

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

Article 8

Communication of information between competent authorities.

1. 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.

Article 9

Traceability

1. Member States shall ensure that tissue establishments or facilities where human application occurs retain the data set out in Annex VI in order to ensure full traceability as established in Article 8 of Directive 2004/23/EC, for at least 30 years in an appropriate and readable storage medium. Data storage may be also in electronic form.

2. To ensure that all human tissues and cells are traceable from donor to recipient or disposal, and vice versa, tissue establishments shall:
   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 human application, research purposes or for manufacturing);

3. Tissue establishments, except in the case of partner donation of reproductive cells, 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.

Article 10

European Coding System

1. Except in the case of partner donation of reproductive cells, a single European identifying code shall be allocated at the tissue establishment, to ensure proper identification of the donor, the traceability of all donated material and to provide information on the main characteristics and properties of tissues and cells. The code shall incorporate at least the information listed in Annex VII.

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.

Article 11

Transposition

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by …….. , 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.

   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 twentieth day following that of its publication in the *Official Journal of the European Union.*

Article 13

Addressees

This Directive is addressed to the Member States.

Done at Brussels,

For the Commission

Member of the Commission

ANNEX I

General Criteria for accreditation, designation, authorisation or licensing of tissue establishments as referred to in Article 2.2

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 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 activities and the clinical outcomes of applied tissues and cells and to interact 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 to the procedures, environment, etc. specific to the tissue establishment.

6. 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.

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. 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 must be transferred to other tissue establishments as specified in Article 21.5 of Directive 2004/23/EC.

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.

10. There must be agreements and procedures in place to ensure that, in the event of termination of activities for whatever reason, the traceability data and other relevant

data concerning the quality and safety of cells and tissues must be transferred to other tissue establishments or to the competent authority.

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.

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 and legal context of their work.

¨NOTE to the minutes on Guidelines for training inspectors

C. Equipment and materials

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

2. All critical equipment and technical devices must be defined 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 the relevant Directives, namely Directive 98/79/EC on in vitro diagnostic medical devices and 93/42 on Medical Devices.

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 must 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 must 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 with a background environment appropriate for the processing of the tissue/cell concerned

4. A less stringent environment may be acceptable where:

   (a). A validated microbial inactivation or terminal sterilisation process is applied after placing in the final container

   (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).

   In (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, immune status of the recipient. . [In all cases a minimum of grade D must be required]

5. 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, 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. 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 must be allocated in both quarantine and released storage locations for holding certain tissue and cells collected in compliance with special criteria (e.g Autologous/allogeneic directed donations or known infective material).

9. The Tissue establishment must have written policies and procedures for controlled access, cleaning and maintenance, waste disposal and emergency situations of facilities.

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 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, 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 adjustments 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 hand-written or transferred to another validated 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, must be kept so as to ensure access to these data for [10 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 must be restricted to persons

authorised by the responsible person, and to the Competent Authority for the purpose of inspection and control measures.

F. Quality review

1. An audit system including self-inspections must 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 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 determined 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.

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

ANNEX II
Criteria for accreditation, designation, authorisation, licensing of tissue and cell preparation processes at the tissue establishments as referred to in Article 3 (2)

FR: Note to the minutes on the need to elaborate detailed technical requirements for each preparation process

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 (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 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 data gained from validation activities to which own previously published data can be added. [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 must be documented in SOPs which must conform to the validated method and to the standards laid down in this Directive, accordingly with points 2.E.1.4.

4 It must 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. Before implementing any significant change in processing the modified process must be validated and documented.

8. The processing procedures must undergo regular critical evaluation to ensure that they continue to achieve the intended results.

9. Special procedures must 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 must 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 must 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 must 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 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 rejected products.

4. Records must 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 within the Tissue establishment not directly involved in tissue and cell processing. If a computer is used to release results from the laboratory, an audit trail should indicate who was responsible for their release.

5. Documented procedures should be in place for the exceptional release of tissues and cells that do not conform to the requirements of this Directive or the Commission Directive on donation, procurement and testing. Exceptional release should be based on certain criteria including an assessment of: the urgency of the request, the availability of test results, the importance of information that is not yet available and the availability of alternative tissues or cells for the recipient. Documentation of exceptional release should include a statement by the recipient´s physician confirming agreement to the use of tissues and cells despite the documented non conformance. The physician must be provided with information that becomes available after exceptional release that is relevant to the quality of the tissues and cells.

6. A Risk Assessment must be undertaken to determine the fate of all stored tissues and cells following the introduction of any new donor selection or testing criteria or any new 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. The container must be inviolable.

2. The container/ package 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 [the tissue establishment must validate that the shipping container comply] relevant critical parameters for the protection of tissue and cell quality must 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. 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.

7. Procedures must 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 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) Expiration date

d) In the case of autologous donation, this has to be specified (for autologous use only) and the 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, the following indication: BIOLOGICAL HAZARD;

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

2. The following information must 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 (tissues, cells, serum, ect…) 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.

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

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 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) 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).

ANNEX III

NOTIFICATION OF SERIOUS ADVERSE REACTIONS

Rapid notification for suspected serious adverse reactions

PART A

Tissue establishment
Report identification
Reporting date (year/month/day)
Individual affected (recipient or living donor)
Date and place of procurement or human application (year/month/day)
Donor identification
Date of suspected serious adverse reaction (year/month/day)
Type of tissues and cells involved in the suspected serious adverse reaction.
Type of suspected serious adverse reaction(s)

PART B

Confirmation for serious adverse reactions

Tissue 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) **If Yes, *Specify***
Clinical outcome (if known) – **Complete recovery** – **Minor sequelae** – **Serious sequelae** – **Death**
Outcome of the investigation and final conclusions

ANNEX IV

NOTIFICATION OF SERIOUS ADVERSE EVENTS

PART A

Tissue 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**			
	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
Report identification
Conclusion 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

(To be developed)

ANNEX VI

Records on traceability as provided for in Article 9

BY TISSUE ESTABLISHMENTS

a) Donor identification

b) Donation identification that will include at least:

- Identification of the procurement organisation or 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.)
- Description and origin of the products and materials 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

d) Final destination Human Application identification will include at least:

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

BY FACILITIES

a) Recipient identification will include at least:

- Identification of the supplier tissue establishment
- Identification of the Clinician or end user / Facility
- Type of tissues and cells
- Product identification
- Identification of the recipient

Date of application

ANNEX VII

Information contained in the European Coding System

a) Donation identification:

- Unique ID number
- Identification of the Tissue establishment

b) Product identification:

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