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.

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.

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**[**F1;**]**

(g) **[**F2Single 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.**]**

Textual Amendments

F1 Substituted by Commission Directive (EU) 2015/565 of 8 April 2015 amending Directive 2006/86/EC as regards certain technical requirements for the coding of human tissues and cells (Text with EEA relevance).

F2 Inserted by Commission Directive (EU) 2015/565 of 8 April 2015 amending Directive 2006/86/EC as regards certain technical requirements for the coding of human tissues and cells (Text with EEA relevance).

[F1If 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.**]**

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)**[**F1;**]**

(j) **[**F2for imported tissues and cells, the country of procurement and the exporting country (if different from the procurement country).**]**

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).