

**Proposal for a Directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells**

(2002/C 227 E/28)

COM(2002) 319 final — 2002/0128(COD)

*(Submitted by the Commission on 19 June 2002)*

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 152(4)(a) thereof,

Having regard to the proposal from the Commission,

Having regard to the opinion of the Economic and Social Committee,

Having regard to the opinion of the Committee of the Regions,

Acting in accordance with the procedure laid down in Article 251 of the Treaty,

Whereas:

- (1) The extensive therapeutic use of human tissues and cells for application in the human body demands that their quality and safety be ensured in order to prevent the transmission of diseases.
- (2) The availability of tissues and cells of human origin used for therapeutic purposes is dependent on Community citizens who are prepared to donate them. In order to safeguard public health and to prevent the transmission of infectious diseases by these tissues and cells, all precautionary measures need to be taken during their procurement, processing, storage, distribution and use.
- (3) There is an urgent need for a unified framework in order to ensure high standards of quality and safety with respect to the procurement, testing, processing, storage and distribution of tissues and cells across the Community and to facilitate exchanges for the thousand of patients receiving this type of therapy each year. It is essential,

therefore, that whatever their intended use, Community provisions should ensure that tissues and cells of human origin are of comparable quality and safety. The establishment of such standards, therefore, will help to reassure the public that human tissues and cells that are procured in another Member State, nonetheless, carry the same guarantees as those in their own country.

- (4) It is necessary to regulate the donation, procurement, and testing of all sources of human tissues and cells intended for application in the human body. The processing, preservation, storage and distribution of all human tissues and cells used for transplantation purposes should also be regulated. However, cells for autologous use should be excluded from the scope if they are to be used for the manufacturing of medicinal products. Tissues and allogeneic cells intended to be used for industrially manufactured products, including medical devices, should be covered only as far as donation, procurement and testing are concerned. The further manufacturing steps are covered by the relevant legislation <sup>(1)</sup>.

- (5) The proposal excludes blood and blood products (other than haematopoietic progenitor cells), human organs, as well as organs, tissues, or cells of animal origin. Blood and blood products currently are regulated by Directive 2001/83/EC <sup>(1)</sup>, Directive 2000/70/EC <sup>(2)</sup> and Council Recommendation 98/463/EC <sup>(3)</sup>, and a new directive based on public health principles is currently under discussion in Council and the European Parliament <sup>(4)</sup>. Tissues and cells used as an autologous graft (tissues removed and transplanted back to the same person), within the same surgical procedure and without being subjected to any banking process, are also excluded from this proposal. The quality and safety considerations associated with this process are completely different.

<sup>(1)</sup> Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).

<sup>(2)</sup> Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000 amending Council Directive 93/42/EEC as regards medical devices incorporating stable derivatives of human blood or human plasma (OJ L 313, 13.12.2000, p. 22).

<sup>(3)</sup> Council Recommendation of 29 June 1998 on the Suitability of blood and plasma donors and the screening of donated blood in the European Community (OJ L 203, 21.7.1998, p. 14).

<sup>(4)</sup> Proposal for a Directive of the European Parliament and of the Council setting standards of quality and safety for the collection, testing, processing, storage, and distribution of human blood and blood components and amending Council Directive 89/381/EEC. COM(2000) 816 final — 2000/0323(COD).

- (6) This Directive does not cover research using human tissues and cells, such as when used for purposes other than application to the human body, i.e. *in vitro* research or in animal models. Only those cells and tissues that in clinical trials are applied to the human body should comply with the quality and safety standards laid down in this Directive.
- (7) This Directive does not interfere with decisions made by Member States concerning the use or non-use of any specific type of human cells, including germ cells and embryonic stem cells. If, however, any particular use of such cells is authorised in a Member State, this Directive will require the application of all provisions necessary to protect public health and guarantee respect for fundamental rights. Moreover, this Directive does not interfere with provisions of Member States defining the legal term 'person' or 'individual'.
- (8) The donation, procurement, processing, preservation, storage and distribution of human tissues and cells for transplantation should comply with high standards of quality and safety in order to ensure a high level of health protection in the Community. This Directive should establish standards for each one of the steps in the human tissues and cells transplantation process.
- (9) It is necessary to increase confidence among the Member States in the quality and safety of donated tissues and cells, in the health protection of living donors and respect for deceased donors, and in the safety of the transplantation process.
- (10) Tissues and cells used for allogeneic therapeutic purposes can be procured from both living and deceased donors. In order to ensure that the health status of a living donor is not affected by the donation, a prior medical examination is required. The dignity of the deceased donor has to be respected.
- (11) The use of tissues and cells for application in the human body can cause diseases and unwanted effects. Most of these can be prevented by careful donor evaluation and the testing of each donation in accordance with rules established and updated according to the best available scientific advice.
- (12) As a matter of principle, tissue and cell transplantation programmes should be founded on the philosophy of voluntary and unpaid donation, anonymity of both donor and recipient, benevolence of the donor and encouragement of the absence of profit by establishments involved in tissue and cell transplantation services.
- (13) The procurement of human tissues and cells must fully respect the Charter of Fundamental Rights of the European Union <sup>(1)</sup>, and take fully into account the principles of the Convention on Human Rights and Biomedicine of the Council of Europe <sup>(2)</sup>, in particular in relation to donor consent.
- (14) All necessary measures need to be taken in order to provide prospective donors of tissues and cells with assurances regarding the confidentiality of any health-related information provided to the authorised personnel, the results of tests on their donations, as well as any future traceability of their donation.
- (15) Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and the free movement of such data <sup>(3)</sup>, applies to personal data processed in application of the present directive. Article 8 of this Directive prohibits in principle the processing of data concerning health. Limited exemptions to this prohibition principle are foreseen. Directive 95/46/EC provides also that the controller must implement appropriate technical and organisational measures to protect personal data against accidental or unlawful destruction or accidental loss, alteration, unauthorised disclosure or access and against all other unlawful forms of processing.
- (16) An accreditation system for tissue banks and a system for notification of adverse events and reactions linked to the procurement, processing, testing, storage, and distribution of tissues and cells of human origin should be established in Member States.
- (17) Member States should organise inspection and control measures, to be carried out by officials representing the competent authority, to ensure compliance of the tissue establishments with the provisions of this Directive.
- (18) Personnel directly involved in the donation, procurement, testing, processing, preservation, storage and distribution of tissues and cells of human origin should be appropriately qualified and provided with timely and relevant training. The provisions laid down in this Directive as regards training should be applicable without prejudice to existing Community legislation on the recognition of professional qualifications.

<sup>(1)</sup> OJ C 364, 18.12.2000, p. 1.

<sup>(2)</sup> Council of Europe. Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: Convention on human rights and biomedicine. European Treaty Series — No 164. Oviedo, 4.4.1997, p. 11.

<sup>(3)</sup> OJ L 281, 23.11.1995, p. 31.

- (19) An adequate system to ensure the traceability of tissues and cells of human origin should be established; traceability should be enforced through accurate substance, donor, recipient, tissue bank, and laboratory identification procedures as well as record maintenance and an appropriate labelling system.
- (20) In order to increase the effective implementation of the provisions adopted under this Directive, it is appropriate to provide for penalties to be applied by Member States.
- (21) Since the objectives of the proposed action, namely to set high standards of quality and safety for human tissues and cells throughout the Community cannot be sufficiently achieved by the Member States alone and can therefore, by reason of scale and effects, be better achieved at Community level, the Community may adopt measures in accordance with the principles of subsidiarity as set out in Article 5 of the Treaty. In accordance with the principle of proportionality, as set out in that Article, this Directive does not go beyond what is necessary for this purpose.
- (22) It is necessary that the best possible scientific advice is available to the Community in relation to the safety of tissues and cells; in particular in order to assist the Commission in adapting the provisions of this Directive to scientific and technical progress.
- (23) The opinions of the Scientific Committee for Medicinal Products and Medical Devices and that of the European Group on Ethics in Science and New Technologies, have been taken into account as well as international experience in this field, and will be sought in the future whenever necessary.
- (24) Since the measures necessary for the implementation of this Directive are measures of general scope within the meaning of Article 2 of Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission <sup>(1)</sup>, they should be adopted by use of the Regulatory Procedure provided for in Article 5 of that Decision,

HAVE ADOPTED THIS DIRECTIVE:

#### CHAPTER I

#### GENERAL PROVISIONS

##### Article 1

##### Objective

This Directive lays down standards of quality and safety of human tissues and cells used for application to the human

body, in order to ensure a high level of protection of human health

#### Article 2

##### Scope

1. The provisions of this Directive shall apply to the donation, procurement, and testing of human tissues and cells for application to the human body. The provisions of this Directive shall also apply to the processing, preservation, storage and distribution of human tissues and cells when they are to be used for human transplantation.

In the case of industrially manufactured products derived from tissues and cells, this Directive applies only to donation, procurement and testing.

2. This Directive does not apply to:

- (a) tissues and cells used as an autologous graft within the same surgical procedure;
- (b) autologous cells to be used for the manufacturing of medicinal products;
- (c) blood and blood components as defined by [Directive of the European Parliament and of the Council setting standards of quality and safety for the collection, testing, processing, storage, and distribution of human blood and blood components and amending Council Directive 89/381/EEC];
- (d) organs.

#### Article 3

##### Definitions

For the purposes of this Directive:

- (a) 'Cells': shall mean individual cells or a collection of cells when not bound by any form of connective tissue.
- (b) 'Tissue': shall mean all constituent parts of the human body formed by cells.
- (c) 'Donor': shall mean a living or deceased individual, including *non-natus*, who is the source of cells or tissues.
- (d) 'Organ': shall mean a differentiated and vital part of the human body, formed by different tissues, that maintains its structure, vascularisation, and capacity to develop physiological functions with an important level of autonomy.
- (e) 'Procurement': shall mean a process by which the donated tissue or cells become available.

<sup>(1)</sup> OJ L 184, 17.7.1999, p. 23.

- (f) 'Processing': shall mean all operations involved in the preparation, manipulation, preservation and packaging of tissues or cells for transplantation.
- (g) 'Preservation': shall mean the use of chemical agents, alterations in environmental conditions or other means during processing to prevent or retard biological or physical deterioration of cells or tissues.
- (h) 'Quarantine': shall mean the status of retrieved tissue or cells or packaging material, or tissue isolated physically or by other effective means whilst awaiting a decision on their release or rejection.
- (i) 'Distribution': shall mean transportation and delivery of tissues or cells for storage, processing or use in recipients.
- (j) 'Transplantation': shall mean the process of reconstituting a function by transferring equivalent cells and/or tissues to a recipient.
- (k) 'Serious adverse event': shall mean 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 results in, or prolongs, hospitalisation or morbidity.
- (l) 'Serious adverse reaction': shall mean an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or transplantation of tissues and cells that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalisation or morbidity.
- (m) 'Tissue bank': shall mean the establishment, public or private, that is responsible for the activities of processing, preservation, storage, and distribution of tissue and cells. It may also be responsible for the procurement of tissues and cells.
- (n) 'Tissue establishment': shall mean a tissue bank or health care establishment that hosts a tissue procurement team.
- (o) 'Tissue procurement team': shall mean the health care professionals involved in any of the activities necessary for tissue and cell procurement.
- (p) 'Allogeneic use': shall mean cells or tissues transplanted from one person to another.
- (q) 'Autologous use': shall mean cells or tissues removed from and transplanted back to the same person.

#### Article 4

#### Implementation

1. Member States shall designate the competent authority or authorities responsible for implementing the requirements of this Directive.
2. This Directive shall not prevent a Member State from maintaining or introducing more stringent protective measures that comply with the provisions of the Treaty.
3. In carrying out the activities covered by this Directive, the Commission may have recourse to technical and/or administrative assistance to the mutual benefit of the Commission and of the beneficiaries, relating to identification, preparation, management, monitoring, audit and control, as well as to support expenditure.

#### CHAPTER II

#### OBLIGATIONS ON MEMBER STATES AUTHORITIES

#### Article 5

#### Supervision of tissue procurement

1. Member States shall take all necessary measures to ensure that tissue procurement teams are either part of a tissue bank or a health care establishment duly accredited and inspected.
2. Member States shall take all necessary measures to ensure that tissue procurement teams are notified to the competent authority and that the procurement, including the staff involved, complies with the requirements listed in Part A of Annex I.

#### Article 6

#### Accreditation of tissue banks

1. Member States shall ensure that all activities relating to the processing, preservation, storage, and distribution of human tissues and cells for human transplantation are undertaken only by tissue banks that have been accredited by a competent authority for that purpose.
2. Haematopoietic progenitor cells from peripheral blood, umbilical cord and bone marrow, however, may be distributed directly from the health care establishment where the procurement is carried out, which could not be accredited as a tissue bank, to a health care establishment for immediate transplantation.
3. The competent authority, having verified that the tissue bank complies with the requirements set out in Annex I, shall accredit the tissue bank and indicate which activities it may undertake and which conditions apply.

4. The tissue bank shall not undertake any substantial changes to its activities without the prior written approval of the competent authority.

5. The competent authority may suspend or revoke the accreditation of a tissue bank if inspection or control measures demonstrate that it does not comply with the requirements of this Directive.

#### Article 7

### Register of accredited tissue banks and reporting obligations

1. The competent authority shall establish and maintain a publicly accessible register of tissue banks specifying the activities for which they have been accredited.

2. Tissue banks shall maintain an official record on the origin and destination of the tissues and cells processed for application in the human body. An annual report of these activities shall be submitted to the competent authority.

3. Member States and the Commission shall establish a network of the national tissue bank registers.

#### Article 8

### Inspection and control measures

1. Member States shall ensure that the competent authority organises inspections and that tissue banks carry out appropriate control measures in order to ensure that the requirements of this Directive are complied with.

2. The competent authority shall also organise inspections and ensure that appropriate control measures are in place in health care establishments where the procurement of human tissues and cells is carried out, as well as in establishments of third parties as specified in Article 24.

3. Inspections and control measures shall be organised by the competent authority on a regular basis. The interval between two inspections and control measures shall not exceed two years.

4. Inspections and control measures shall be carried out by officials representing the competent authority who must be empowered to:

(a) inspect health care establishments involved in procurement, accredited tissue banks, as well as the facilities of any third parties;

(b) evaluate the procedures and the activities carried out by the health care establishments, tissue banks and the facilities of third parties;

(c) examine any documents relating to the subject of the inspection.

5. The competent authority shall organise inspections and other control measures as appropriate in the event of any serious adverse reaction or serious adverse event.

6. Member States shall, upon the request of another Member State or the Commission, provide information about the results of inspections and control measures carried out in individual tissue banks, healthcare establishment or the facilities of third parties.

#### Article 9

### Import/export of human tissues and cells

1. Member States shall take all necessary measures to ensure that all imports of human tissues or cells from third countries are approved by the competent authority. All tissues and cells that are exported to third countries shall comply with the requirements of this Directive.

2. The import/export of human tissues and cells for transplantation shall be undertaken only through accredited tissue banks.

3. The competent authority shall approve imports of human tissues and cells from third countries only when equivalent standards of quality and safety to the ones laid down in this Directive are ensured.

4. The procedures for verifying the equivalent standards of quality and safety in accordance with paragraph 3 shall be established by the Commission in accordance with the procedure referred to in Article 30(2).

#### Article 10

### Traceability

1. Member States shall ensure that tissue establishments take all necessary measures to ensure that all tissues and cells procured, processed, stored and distributed on their territory can be traced from the donor to recipient and vice versa.

2. The procedures for ensuring traceability at the Community level shall be established by the Commission according to the procedure referred to in Article 30(2).

3. Tissue establishments shall implement a donor identification system and assign a code to each donation and its products.

4. All tissues and cells must be identified with a label that contains the information listed in Annexes VI and VII.

*Article 11***Notification of serious adverse events and reactions**

1. The Member States shall ensure that there is a system in place to report, register, and transmit information about serious adverse events and reactions related to the procurement, testing, processing, storage, distribution and transplantation of tissues and cells.
2. The responsible person referred to in Article 17 shall notify the competent authority of any serious adverse events and reactions referred to in paragraph 1 and provide a report analysing the cause and the ensuing outcome.
3. The procedure for notifying adverse events and reactions shall be established by the Commission in accordance with the procedure referred to in Article 30(2).

## CHAPTER III

**DONOR SELECTION AND EVALUATION***Article 12***Principles for tissue and cell donation**

1. Member States shall encourage voluntary and unpaid donations of tissues and cells with a view to ensuring that they are in so far as possible provided from such donations
2. Member States shall take all necessary measures to ensure that any promotion and publicity activities in support of the donation of human tissues and cells receive prior approval by the competent authority. Advertising the need for, or availability of, human tissues and cells, with a view to offering or seeking financial gain or comparable advantage shall be prohibited.
3. Member States shall encourage that the procurement of tissues and cells is carried out on a non-profit basis.

*Article 13***Consent**

1. The procurement of human tissues or cells shall be carried out only after all mandatory consent requirements in force in the Member State are met.
2. Member States shall take all necessary measures to ensure that the recipients, donors or their families are provided with the information listed in Annex III.

*Article 14***Data protection and confidentiality**

1. Member States shall take all necessary measures to ensure that all data, including genetic information, collated within the scope of this Directive and to which third parties have access have been rendered anonymous so that the donor and the recipient are no longer identifiable.
2. For that purpose, they shall ensure that:
  - (a) data security measures are in place as well as safeguards against any unauthorised data additions, deletions, or modifications to donor files or deferral records, as well as any transfer of information;
  - (b) procedures are in place to resolve data discrepancies; and
  - (c) no unauthorised disclosure of information occurs, whilst guaranteeing the traceability of donations.
3. Member States shall take all necessary measures to ensure that the identity of the recipient(s) is not disclosed to the donor or his family and vice versa, without prejudice to legislation in force in Member States on the conditions of disclosure if the donor is closely related to the recipient.

*Article 15***Selection, evaluation, and procurement**

1. The tissue procurement team shall ensure that the donor evaluation and selection is carried out according to the requirements specified in Annex IV.
2. The tissue procurement team shall ensure that tissues and cells are procured, packaged and transported to the tissue banks in accordance with Annex VI.
3. In the case of an autologous donation, the suitability criteria shall be established and documented by the physician responsible for the patient, according to the clinical record, the therapeutic indication, and in accordance with the requirements listed in point 2.1 of Annex IV.
4. The tissue banks shall ensure that the selection and acceptance of tissues and cells comply with the requirements of Annex VI. They shall also ensure that all donations are tested in accordance with Annex V.
5. The results of the donor evaluation and testing procedures shall be documented and any relevant abnormal findings shall be reported in accordance with Annex III.

6. The competent authority shall ensure that all the activities related to tissue procurement shall be carried out in accordance with the conditions specified in Annex VI.

#### CHAPTER IV

### PROVISIONS FOR QUALITY AND SAFETY IN TISSUE PROCESSING

#### Article 16

#### Quality management

1. Member States shall take all necessary measures to ensure that each tissue establishment sets up and maintains a quality management system.

2. The Commission shall establish in accordance with the procedure laid down in Art 30(2) the Community standards and specifications, referred to in Annex II, for the activities relating to a quality management system.

3. Tissue establishments shall take all necessary measures in order to ensure that the quality management system includes at least the following documentation:

- Standard Operating Procedures;
- Guidelines;
- Training and reference manuals;
- Reporting forms;
- Donor records.

4. Tissue establishments shall take all necessary measures to ensure that this documentation is available for official inspections.

5. Tissue establishments shall keep donor records for a minimum of 30 years after the confirmed clinical use of the last tissue/cell.

#### Article 17

#### Responsible person

1. Tissue banks shall designate a responsible person. This person shall fulfil the following minimum conditions and qualifications:

- (a) he/she shall possess a diploma, certificate or other evidence of formal qualifications in the field of medical or biological sciences awarded on completion of a university course of study or a course recognised as equivalent by the Member State concerned;

- (b) he/she shall have at least two years practical experience, in one or more tissue banks accredited in accordance with Article 6.

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

- (a) ensuring that every unit of tissues and cells of human origin has been procured and tested for application in the human body and processed, stored, and distributed, when intended for transplantation, in compliance with the laws in force in the Member State;
- (b) providing information to the competent authority as required in Article 6;
- (c) implementing the requirements of Articles 7, 10, 11, 15, 16, and 18 to 25 in the tissue bank.

3. Tissue banks shall notify the competent authority of the name of the responsible person referred to in paragraph 1. Where the responsible person is permanently or temporarily replaced, the tissue bank shall provide immediately to the competent authority the name of the new responsible person and his or her date of commencement.

#### Article 18

#### Personnel

Personnel directly involved in activities related to the procurement, processing, preservation, storage and distribution of tissues and cells in a tissue establishment shall be qualified to perform such tasks and shall be provided with the relevant training specified in Annex II.

#### Article 19

#### Tissue and cell reception

1. The tissue bank shall ensure that human tissue and cells and associated documentation comply with the requirements listed in Annex VI. The documentation to be verified for each tissue or cell is listed in Parts D and E of Annex VI.

2. The tissue bank shall ensure and record the fact that the packaging conditions of the human tissue and cells received comply with the provisions listed in Annex VI. Any tissues and cells that do not comply with these provisions should be discarded in accordance with Annex VI.

3. The acceptance or rejection of the incoming tissues/cells shall be documented.

4. Tissue banks shall ensure that human tissues and cells are correctly identified at all times. Each delivery or batch of tissues or cells must be assigned an identifying code, in accordance with Article 10.

*Article 20***Tissue and cell processing**

1. The tissue bank shall include in its Standard Operating Procedures all the processing that directly affect quality and safety, and shall ensure that they are carried out under controlled conditions. The tissue bank shall ensure that the equipment used, the working environment, process design, validation, and control conditions are in compliance with Annex VII.

2. Any modifications to the processes used in the preparation of the tissues and cells shall also meet the criteria laid down in paragraph 1.

3. The tissue bank must make special provisions in its Standard Operating Procedures for the handling of tissues and cells to be discarded in order to prevent the contamination of other tissues or cells, the processing environment, or personnel.

*Article 21***Tissue and cell storage conditions**

1. Tissue banks shall ensure that all procedures associated with the storage of tissues and cells are documented in the Standard Operating Procedures and that the storage conditions comply with requirements listed in Annex VII.

2. Tissue banks shall ensure that all storage processes are carried out under controlled conditions.

3. Tissue banks shall establish and maintain procedures for the control of packaging and storage areas, in order to prevent any condition that might adversely affect the function or integrity of tissue and cells.

4. Processed tissues or cells must be held in quarantine until released by the responsible person referred to in Article 17. Tissues or cells must not be released from quarantine for preservation and storage until all the requirements laid down in the Standard Operating Procedures have been met.

*Article 22***Labelling, user information and packaging**

Tissue banks shall ensure that labelling, documentation, and packaging conform to the requirements listed in Annex VII Parts D and E.

*Article 23***Transport and distribution**

The tissue bank shall guarantee the quality of tissues or cells until delivery. Distribution conditions shall comply with the requirements listed in Annex VII.

*Article 24***Relationship of tissue banks with third parties**

1. A tissue bank shall establish a written agreement with a third party in the following circumstances:

- (a) where a third party takes responsibility in one phase of tissue or cell processing on behalf of the tissue bank;
- (b) where a third party provides goods and services that affect tissue or cell quality and safety assurance;
- (c) where a tissue bank provide services to another tissue bank;
- (d) where a tissue bank distributes tissue or cells processed by third parties.

2. The tissue bank shall evaluate and select third parties on the basis of their ability to meet the standards laid down in this Directive.

3. Tissue banks shall notify to the competent authority the complete list of agreements that they have established with third parties.

4. The agreements between tissue bank and third parties shall specify responsibilities to be carried out by the third party and detailed procedures.

5. Tissue banks shall provide copies of agreements with third parties when required by the competent authority.

*Article 25***Access to human tissues and cells**

1. Member States shall ensure that public and private establishments involved in health care, and establishments authorised to manufacture medicinal products or medical devices, have access to human tissue and cells, without prejudice to the provisions in force in Member States on the use of certain tissues and cells.

2. Such establishments shall report relevant information to the tissue banks in order to facilitate traceability, and ensure quality control and safety.

## CHAPTER V

**EXCHANGE OF INFORMATION, REPORTS, AND PENALTIES***Article 26***Coding of information**

1. Member States shall establish a system for the identification of human tissues and cells, in order to ensure the traceability of all human tissues and cells, as indicated in Article 10.

2. The Commission, in cooperation with Member States, shall design a single European coding system that will provide the basic description and properties of tissues and cells.

*Article 27*

### **Reports**

1. Member States shall send the Commission, three years after the implementation date indicated in Article 32(1), and every three years thereafter, a report on the activities undertaken in relation to the provisions of this Directive, including an account of the measures taken in relation to inspection and control.

2. The Commission shall transmit to the European Parliament, the Council, the Economic and Social Committee, and the Committee of the Regions, the reports submitted by the Member States on the experience gained in implementing this Directive.

*Article 28*

### **Penalties**

Member States shall lay down the rules on penalties applicable to infringements of the national provisions adopted pursuant to this Directive and shall take all measures necessary to ensure that they are implemented. The penalties provided for must be effective, proportionate, and dissuasive. Member States shall notify those provisions to the Commission by the date specified in Article 33(1) at the latest and shall notify it without delay of any subsequent amendments affecting them.

CHAPTER VI

## **CONSULTATION OF COMMITTEES**

*Article 29*

### **Adaptation to technical and scientific progress**

The adaptation of the technical requirements set out in Annexes I to VII to technical and scientific progress shall be decided by the Commission in accordance with the procedure referred to in Article 30(2).

*Article 30*

### **Regulatory procedure**

1. The Commission shall be assisted by a Committee, composed of representatives of the Member States and chaired by the representative of the Commission.

2. Where reference is made to this paragraph, Articles 5 and 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

3. The period referred to in Article 5(6) of Decision 1999/468/EC shall be set at three months.

4. The Committee shall adopt its rules of procedure.

*Article 31*

### **Consultation of scientific committee**

The Commission may consult the relevant scientific committee when adapting the Annexes of this Directive to scientific and technical progress.

CHAPTER VII

## **FINAL PROVISIONS**

*Article 32*

### **Transposition**

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive not later than ... They shall forthwith inform the Commission thereof.

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

2. Member States may decide for one year after the date laid down in the first subparagraph of paragraph 1, not to apply the requirements of this Directive to tissue banks operating under national provisions before the entry into force of this Directive.

3. Member States shall communicate to the Commission the texts of the provisions of national law that they have already adopted or which they adopt in the field governed by this Directive.

*Article 33*

### **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 Communities*.

*Article 34*

### **Addressees**

This Directive is addressed to the Member States.

## ANNEX I

## A. REQUIREMENTS FOR THE PROCUREMENT OF HUMAN TISSUES OR CELLS

The establishment responsible for tissue and cells procurement has to ensure certain minimum requirements and other conditions. It must:

- (a) Have links with a medical/surgical team that specialises in cell/tissues procurement, and has the staff with the necessary training and experience required to do this work;
- (b) Have a cooperation agreement with the team responsible for donations. The written contractual documents will specify the terms of the relationship as well as the protocols to be followed;
- (c) Have Standard Operation Procedures (SOPs) for the procurement, packaging, and transportation of the cells and/or tissues until the moment they are processed;
- (d) Have a quality management system;
- (e) Ensure that, in addition to the tests described in Annex V, appropriate investigations are carried out to prevent the presence of known transmissible diseases;
- (f) Have the facilities and material resources needed for the procurement and packaging of the cells and/or tissues;
- (g) Have the staff and services needed for body reconstruction and other mortuary procedures when cell/tissue are retrieved from a deceased person;
- (h) Ensure that the procedures for the procurement or collection of the cells and/or tissues are carried out according to Annex VI;
- (i) Maintain a register to ensure adequate traceability of the cells/tissues obtained and delivered. Details must be maintained on the procurement procedures, the donor (donor identification, consent and clinical data), the tissues donated, the intended use or destination of the tissues, the date of removal and the tests carried out. Access to this register will be restricted to persons, authorised by the responsible person, who will be required to comply with the confidentiality requirements laid down in the Directive.

## B. CRITERIA FOR ACCREDITATION OF TISSUE BANKS

In order to be accredited, tissue banks must:

- (a) Have an organisational structure and operational procedures appropriate to the activities for which accreditation is sought, ensuring that it is able to receive, distribute, and allocate tissues and cells for transplantation on a 24 hour basis;
  - (b) Have documentation showing the links that will be maintained with third parties (medical and non-medical institutions) with which the bank will collaborate. Third party agreements will specify the terms of the relationship as well as the protocols to be followed;
  - (c) Have staff with adequate training and suitable facilities to carry out the activities for which accreditation is sought, in accordance with the standards laid down in this Directive;
  - (d) Have a quality assurance programme relating to the activities for which accreditation is sought, in accordance with the standards laid down in this Directive;
  - (e) Ensure, in accordance with scientific knowledge, that the risks inherent in the use and handling of biological material are minimised;
  - (f) Have access to a serum bank that maintains at least one sample from each allogeneic donor for a minimum period of 2 years from the distribution of the last anatomical piece of the donor, so that required tests can be performed after grafting;
  - (g) Have a register with access restricted to persons authorised by the responsible person in order to ensure adequate traceability of the cells/tissues received and distributed. These records should contain information on all donors, anatomical pieces, and tissues and cells with the data required for their identification. The register must meet the confidentiality requirements laid down in the Directive; and
  - (h) Work according to Standard Operation Procedures, which shall conform to the standards laid down in this Directive.
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## ANNEX II

## QUALITY MANAGEMENT SYSTEM

1. The basic elements of a quality system are:
    - (a) A well-defined quality policy;
    - (b) A clearly-defined organisational structure and accountability;
    - (c) Clearly-defined and effective documentation;
    - (d) Standard Operating Procedures (SOPs);
    - (e) Correct maintenance of all registers; and
    - (f) Process validation by the personnel directly involved.
  2. The main functions of a quality system include but are not limited to:
    - (a) Ensuring that all processes are correct, verified and documented;
    - (b) Ensuring the appropriate analysis and the communication of results to the competent authorities in those cases where: the integrity and function of a human cellular or tissue-based product could be affected, the product could possibly be contaminated, or the product could potentially transmit a communicable disease;
    - (c) Ensuring that, if needed, appropriate corrective actions are taken and registered;
    - (d) Ensuring that the proper training and education are provided to the staff for each of the activities in which they are involved;
    - (e) Establishing and maintaining an appropriate monitoring system;
    - (f) Establishing and maintaining a records system;
    - (g) Investigating and documenting product deviations and the corrective actions taken; and
    - (h) Conducting evaluations, investigations, audits, and other actions necessary to ensure the quality of tissues/cells, products and processes.
  3. The basic and on-going training for staff in charge of tissue/cell procurement and staff of the tissue banks shall be:
    - (a) Carried out within two months of their joining the tissue establishment and after intervals no longer than two years;
    - (b) Carried out when a new activity or a new technology is introduced; and
    - (c) Controlled, reviewed and updated periodically, but at least every two years, and be adequate to their needs.
  4. The on-going training shall cover at least the following subjects:
    - 4.1. General topics:
      - (a) General review of the procedures for obtaining and/or processing human cells and tissues for transplant purposes;
      - (b) Legal aspects;
      - (c) Ethical aspects;
      - (d) Organisational aspects;
      - (e) Quality control programmes;
      - (f) Quality and safety criteria for the evaluation, procurement, processing and monitoring of cells and tissues for transplantation; and
      - (g) Safety at work.
    - 4.2. Specific topics:
      - (a) Technical knowledge and specific protocols for each of the tissue bank's activities;
      - (b) Management of registers and data analysis programmes;
      - (c) Handling of the equipment used for each activity;
      - (d) Knowledge of the quality control guidelines and general operation of the health care establishment;
      - (e) Knowledge of the personal safety guidelines; and
      - (f) Bio-monitoring systems operating at the health care establishment.
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## ANNEX III

**INFORMATION TO BE PROVIDED ON THE DONATION OF CELLS AND/OR TISSUES**

## A. AUTOLOGOUS (AU) AND ALLOGENEIC (AL) LIVING DONORS

1. The person in charge of the donation process shall ensure that the donor has been properly informed of at least those aspects relating to the donation and procurement process outlined in paragraph 4.
2. The information must be given in an appropriate and clear manner, using terms that are easily understood by the donor.
3. The person providing the information must be required and able to answer any questions asked by the donor.
4. The information must cover: the purpose and nature of the procurement, its consequences and risks; analytical tests, if they are performed; recording and protection of donor data, medical confidentiality; and therapeutic purpose.
5. For the allogeneic living donor (AL), information must be provided to the donor on the evaluation procedure: i.e. the reasons for requiring the donor's medical and personal history, a physical examination, and analytical tests.
6. Information must be given to donors on the applicable safeguards that are intended to protect them.
7. The confirmed results of the analytical tests must be communicated, and clearly explained, to the donor.
8. Information must be given on the necessity for requiring the applicable mandatory consent, certification, and authorisation in order that the tissue and/or cell procurement can be carried out.

## B. DECEASED DONOR

1. All information must be given to the donor's relatives and all necessary consents and authorisations must be obtained prior to the procurement of cells/tissues in accordance with the applicable legislation.
2. The confirmed results of the donor's evaluation must be communicated, and clearly explained, to the donor's relatives when these results have relevance for their health or for public health.

## ANNEX IV

**SELECTION CRITERIA FOR THE DONOR OF TISSUES AND/OR CELLS****1. Deceased donor**

## A. GENERAL CRITERIA FOR EXCLUSION

Deceased donors shall be excluded from donation if any of the following conditions are met:

1. Cause of death unknown.
2. Ingestion of, or exposure to, a toxic substance that may be transmitted in a toxic dose to the tissue recipients.
3. Presence or previous history of malignant disease, except for primary basal cell carcinoma, carcinoma *in situ* of the uterine cervix, and some primary tumours of the central nervous system that have to be evaluated according to the current consensus document of the Council of Europe 'Standardisation of organ donor screening to prevent transmission of neoplastic diseases'. Donors with malignant diseases could be evaluated and considered for cornea donation, except for those with retinoblastoma, melanoma of the anterior pole, haematological neoplasm, and malignant tumours that could affect the anterior pole of the eye.
4. Risk of transmission of diseases caused by prions. This includes:
  - specific selection criteria for people diagnosed with Creutzfeldt-Jakob Disease or having family history of non-iatrogenic Creutzfeldt-Jakob Disease;
  - people with a history of rapid progressive dementia or degenerative neurological diseases of unknown origin;
  - recipients of hormones derived from the human pituitary gland (e.g. growth hormones) and recipients of dura mater.

5. Infection which is not controlled at the time of the donation, including bacterial diseases, systemic viral and fungal infections.
6. History, clinical evidence, or confirmed positive laboratory tests of HIV infection, acute or chronic hepatitis B or hepatitis C infection (For haematopoietic progenitor cells donors, Annex V about the donors with positive tests for HBV and HCH shall be applied).
7. People with a history of chronic haemodialysis.
8. Haemodilution of donor samples:  

With potential donors who have received blood, blood components, colloids within the 48 hours preceding death, or crystalloids within the 1 hour preceding death, a sample of blood taken before the transfusion will have to be available if calculations using the algorithm set out below indicate a haemodilution of over 50 %. If a sample is not available, the donor must be excluded owing to the effect of the haemodilution on the results of the serology tests.
9. Evidence of any other risk factors.

#### B. SPECIFIC EXCLUSION CRITERIA FOR CHILD DONORS

1. Any child who may present with any of criteria listed in part A will be excluded as a donor.
2. Any children born from mothers with HIV infection or that meet any of the exclusion criteria described in part A must be excluded as donors until the risk of transmission of infection can be definitely ruled out.
  - (a) Children aged less than 18 months born from mothers with HIV, hepatitis B or hepatitis C infection or at risk of such infection, or who have been breastfed by their mothers during the previous 12 months, cannot be considered as donors regardless of the results of the analytical tests;
  - (b) Children who have not been breastfed by their mothers during the previous 12 months, and for whom analytical tests, physical examinations, and reviews of medical records do not provide evidence of HIV, hepatitis B or hepatitis C infection, can be accepted as donors.

#### C. EXTERNAL PHYSICAL INSPECTION

A physical examination of the body shall be performed to detect any signs that may be sufficient in themselves to exclude the donor, or which may be assessed in the light of the donor's medical and personal history. Attention should be given to the following: tumours (e.g. melanoma), infections (e.g. genital ulcers, anal condylomas), risk factors for transmissible diseases (e.g. vessel puncture, tattoos, piercing), traumas to the donor's body, and scars from recent or old operations.

#### D. SPECIFIC SELECTION CRITERIA

Specific selection criteria for tissues from deceased donors shall be taken into account case by case on the basis of current scientific knowledge.

### 2. Living donor

#### 2.1. Autologous living donor

1. The medical doctor responsible for the patient-donor must determine, based on the patient's medical history and therapeutic indications, and document the viability of the transplant.
2. If the removed cells or tissues are stored or cultured, the same serology tests must be carried out as for an allogeneic living donor. Positive results will not rule out the person undergoing the treatment.

#### 2.2. Allogeneic living donor

1. The selection criteria for the allogeneic living donor shall be established and documented by the responsible physician based on the donor's physical status, clinical and personal record, the results of clinical analyses, and other laboratory tests establishing the donor's health.
  2. The same exclusion criteria as for deceased donors have to be followed, but others may need to be added: e.g. pregnancy (except for donors of haematopoietic progenitor cells and amniotic membrane) and breastfeeding. The specific exclusion criteria for each tissue/cells shall also need to be taken into account.
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## ANNEX V

## LABORATORY TESTS REQUIRED FOR DONORS

## 1. Serology tests required for donors

| Infection  | Tissues and cells: recommendation in case of positive result   |
|--|--|
| HIV 1 and 2  | Contraindication to donation   |
| Hepatitis B  | HBs Ag positive is a contraindication to donation<br>Anti Hbc positive requires complementary tests      |
| Hepatitis C  | Contraindication to donation   |
| Treponema pallidum   | Requires tests to detect specific antibodies for T. pallidum. A positive result contraindicates donation |
| HTLV-I and II in donors living or coming from high incidence areas, or their sexual partners or children | Contraindication to donation   |

## 2. General requirements to be met when determining serological markers

1. The tests should be carried out by a qualified laboratory, authorised by the competent authority in the Member State.
2. The serological tests will be carried out on the donor's serum or plasma; they should not be performed on other fluids or secretions such as the aqueous or vitreous humour.
3. The type of test used shall be in agreement with the scientific knowledge.
4. All blood samples should be obtained immediately prior or after the tissue procurement in case of a deceased donor.
5. In the case of living donors (except allogeneic bone marrow and peripheral blood cells donors, for practical reasons), blood samples should be obtained at the time of donation, with an admitted margin of  $\pm 7$  days and a repeat sample after 6 months.
6. In case of an allogeneic haematopoietic progenitor cell transplantation, blood samples shall be tested within 30 days prior to donation.
7. If in a living donor (except allogeneic haematopoietic progenitor cell donors) the blood sample is drawn 6 days after procurement and tested by nucleic acid amplification technique (NAT), a repeat blood sample is not necessary for HIV, HBV and HCV.

## ANNEX VI

## CELL AND/OR TISSUE PROCUREMENT PROCEDURES, AND RECEPTION AT THE TISSUE BANK

## A. VERIFICATION PROCEDURE

**Consent**

Before the procurement of tissues or cells, the person responsible from the procurement team shall confirm that the consent for the procurement has been obtained according with the legislation in place in the Member State.

**Donor identification**

- (a) Donor and donation data shall be registered and maintained in a manner that ensures correct donor identification and traceability of each individual tissue and cell.
- (b) The data registration system has to be validated to ensure that the recorded information ensures correct identification and traceability.

## B. FACILITIES AND PROCEDURES FOR THE PROCUREMENT OF TISSUES AND CELLS

Donations shall be retrieved in appropriate facilities that minimise bacterial contamination of procured tissues or cells. For living donors, the procurement environment must also ensure their health and safety.

#### C. PROCUREMENT PROCEDURES FOR TISSUES AND CELLS

The procurement procedures shall be appropriate for the type of donor and the type of tissue/cells donated. They should also protect those properties of the tissue/cells that are required for their ultimate clinical use, and at the same time avoid microbiological contamination during the process. In the case of deceased donations, the time interval from death to procurement shall be specified so as to ensure the protection of the required biological properties.

#### D. DONOR DOCUMENTATION

1. For each donor, there should be a dossier that contains: donor identification, the consent form, clinical data, laboratory test results, and results of other tests carried out. Data related with the procurement process shall also be registered.
2. In case an autopsy was carried out, the results shall be included in the dossier.
3. All the records must be legible and permanent and shall be in compliance with data protection legislation.
4. Donor clinical records shall be maintained for at least 30 years in the registry of the procurement establishment.
5. The date and time of procurement (start and end) must be recorded.

#### E. DATA TO BE REGISTERED

The data that must be registered in the tissue bank includes:

- (a) Consent;
- (b) Donor identification and characteristics: type of donor, age, sex, cause of death, and presence of risk factors;
- (c) Review of clinical data against donor selection criteria;
- (d) Results of physical examination, of laboratory tests and of other tests (autopsy report when one was conducted);
- (e) Date and time of the death/perfusion;
- (f) Date and time of the procurement, and health care establishment where the procurement is carried out;
- (g) Conditions under which the cadaver is kept: refrigerated (or not), time of start of refrigeration and time of transfer to procurement site;
- (h) Place of procurement, procurement team, and person in charge of procurement;
- (i) Degree of asepsis;
- (j) Details about the preservation solutions used during procurement, including composition, lot, date of expiry, temperature, amount, concentration and preparation method;
- (k) Grafts obtained and relevant characteristics;
- (l) Relevant incidents that have occurred before, during, and after procurement;
- (m) Destination of the cells/tissues procured;
- (n) Method of preservation until arrival of tissues/cells at the bank;
- (o) In the case of cellular cultures, it is necessary also to document:
  - Characteristics of the lesion to be treated;
  - Medicinal allergies (e.g. antibiotics) of the recipient.

#### F. PACKAGING

1. Following procurement, all donations shall be packed individually in a manner that minimises the risk of contamination and preserves the required characteristics and biological function of the cells/tissues.
2. The packaged cells/tissues shall be shipped in a rigid container suitable for transport, which maintains the integrity of the contents and the specified temperature.
3. Any accompanying tissue or blood samples for testing shall be correctly labelled and identified.

#### G. LABELLING OF THE RETRIEVED TISSUE/CELLS

Every package containing tissues or cells must be labelled at least with:

- (a) Donor identification number or code; and
- (b) Type of tissue/cells.

#### H. LABELLING OF THE SHIPPING CONTAINER

When tissues/cells are shipped, every shipping container must be labelled at least with:

- (a) Identification of the tissue/cells;
- (b) Identification of the procurement establishment (address and phone number) and the person in charge of the delivery;
- (c) Identification of the tissue bank of destination (address and phone number) and the person in charge of the reception at the destination;
- (d) Date and time of harvesting;
- (e) In the cases of haematopoietic progenitors, the following shall be added: DO NOT IRRADIATE; and
- (f) In the case of 'autologous' donors, the following shall be added: 'for autologous use only'.

#### I. RECONSTRUCTION OF CADAVER

Once the tissues have been retrieved, the deceased donor body should be reconstructed so that it is as similar as possible to its original anatomical shape. Reconstruction methods should minimise any impact on normal funeral procedures.

#### J. RECEIPT OF THE TISSUE/CELLS AT THE PROCESSING/STORAGE ESTABLISHMENT

When the retrieved tissues/cells arrive at the processing/storage establishment, there shall be a documented verification that the consignment, including, transport conditions, packaging, labelling and associated documentation and samples, meet the requirements of this Annex and the specifications of the receiving bank. Each bank shall have a documented procedure for handling non-conforming consignments of tissues/cells.

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### ANNEX VII

#### CELL AND TISSUE PROCESSING, STORAGE, AND DISTRIBUTION

##### A. PROCESSING

1. Every tissue and cell processing facility must have an adequate system of process control.
2. When technical procedures cannot be verified at any particular time throughout the process, they must be continuously monitored to ensure that the established Standard Operating Procedures are met.
3. Where a microbial inactivation procedure is applied to the tissue or cells, it must be specified, documented, and validated.
4. Where any processing step is carried out by a third party, an agreement must be documented to demonstrate the required performance specification and validation.
5. The processes should undergo regular critical evaluation to ensure that they continue to achieve the intended results.
6. Before new processes are implemented, they must be validated to demonstrate that they will consistently result in tissues that comply with the SOPs of the tissue bank. Where any significant change in processing occurs, involving new or modified equipment, major overhauls or change of location, these validation steps must be repeated and documented.
7. Environments in which tissues are processed must be adequately controlled to minimise or avoid the potential for tissue contamination. Where tissues or cells are exposed to the environment during processing, without a subsequent microbial inactivation process, an air quality of Grade A (< 3 500 particles per m<sup>3</sup> of minimum 0,5 µm) is required, usually by using a laminar air flow (LAF) cabinet. The background environment must be suitable to maintain a Grade A in the LAF. Where tissues or cells are exposed to the environment during processing with a subsequent microbial inactivation process, a Grade C environment (< 350 000 particles per m<sup>3</sup> of minimum 0,5 µm and < 2 000 particles per m<sup>3</sup> of 5 µm) is required.

**B. STORAGE**

1. Storage conditions, including relevant parameters such as temperature, must be defined to maintain the required tissue and cell properties.
2. Critical parameters (e.g. temperature, humidity, sterility) must be controlled, monitored, and recorded continuously to demonstrate compliance with the specified conditions.
3. Maximum storage time must be specified for each type of storage condition.
4. 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.

**C. DISTRIBUTION**

1. Transport conditions, including relevant parameters such as temperature, must be defined to maintain the required tissue and cell properties.
2. Packaging must ensure that the tissue is maintained in the condition established in the Standard Operating Procedures. If the packaging has not received market validation for this purpose, then critical parameters, such as temperature and humidity must be continuously controlled during the delivery process.
3. Where distribution is carried out by a contracted third party, a documented agreement must be in place to ensure that the required conditions are maintained.
4. A documented system must be in place for the recall of tissue or cells in the event that a potential risk to the recipient(s) is identified following distribution.

**D. FINAL LABELLING FOR DISTRIBUTION**

1. Every unit of tissue/cells distributed has to be accompanied by a label with at least the following information:
  - (a) Identification number or code of the tissue/cells;
  - (b) Characteristics of the tissue or cell;
  - (c) Identification of the tissue bank;
  - (d) Lot number.
2. The following information shall be provided either on the label or in accompanying documentation:
  - (a) Morphology and functional data;
  - (b) Date of distribution of the tissue/cell;
  - (c) Serological determinations carried out on the donor and results;
  - (d) Storage recommendations;
  - (e) Instructions for opening the container, package, and any required manipulation;
  - (f) Expiry date after opening/manipulation; and
  - (g) Instructions on reporting serious adverse reactions and/or events.

**E. EXTERNAL LABELLING OF THE SHIPPING CONTAINER**

Every container shall be labelled with at least the following information:

- (a) Identification of the originating tissue bank;
  - (b) Identification of the health care establishment of destination;
  - (c) A statement that the package contains human tissue/cells;
  - (d) In the case of haematopoietic progenitors, the following shall be added: 'DO NOT IRRADIATE';
  - (e) Recommended transport conditions (e.g. keep cool, in upright position, etc.); and
  - (f) Safety instructions/method of cooling (when applicable) [for instance: liquid N<sub>2</sub> poses a hazard for transport, manipulation of dry ice with bare hands also, etc.].
-