Directions given under the Human Tissue Act 2004: 001/2006

Directions on the standards required under Directive 2004/23/EC dated 31 March 2004 and the first Commission Directive 2006/17/EC thereto.

Ref 001\2006

These Directions are	Given in relation to licences to store tissue for transplantation under section 16(2)(e)(ii)
Section of the Human Tissue Act (HT Act) providing for these directions	Section 23 (1) and (2)
These Directions come into force on	25 April 2006
These Directions remain in force	Until revoked

1. These Directions are made for the purposes of setting down the standards expected of establishments under Directive 2004/23/EC of the European Parliament and 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 (hereafter "the parent directive"), and Commission Directive 2006/17/EC of 8 February 2006 specifying the technical requirements for the donation, procurement and testing of human tissues and cells (hereafter "Commission Directive 2006/17/EC").

2. Establishments shall have until 6 April 2007 to comply with the requirements of the parent directive and Commission Directive 2006/17/EC. Any obligations imposed by these directions insofar as they are required by the provisions of the parent directive or Commission Directive 2006/17/EC shall be read accordingly.

Designated Individual

3. The Designated Individual (DI) shall at least fulfil the following conditions and have the following qualifications:

   a. Possession of 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 England, Wales and Northern Ireland and Scotland; or is otherwise deemed suitably qualified by the Human Tissue Authority (HTA) on the basis of academic qualifications and practical experience in relevant areas of work; and

   b. At least two years' practical experience in the relevant fields.

4. The DI shall have responsibility for:

   a. Ensuring that human tissues and cells intended for human application in the establishment are procured, tested, processed, stored and distributed in accordance with the parent directive and Commission Directive 2006/17/EC;

   b. Ensuring that the establishment carries out all appropriate control measures as required from time to time by the HTA to ensure compliance with the parent directive and Commission Directive 2006/17/EC;

   c. Keeping a record of the establishment's activities in accordance with paragraph 57 (a) and submitting to the HTA an annual report on these activities;

   d. Notifying the HTA of any serious adverse event and/or serious adverse reaction and providing the HTA with a report analysing the cause and ensuing outcome;

   e. Ensuring that the selection, evaluation or procurement of tissue or cells intended for human application are carried out in compliance with the parent directive and Commission Directive 2006/17/EC;

   f. Ensuring that the establishment puts in place and updates a quality management system in accordance with paragraph 20;

   g. Ensuring that personnel directly involved in the procurement, processing, preservation, storage and distribution of tissues and cells are qualified to perform such tasks and are provided with the necessary training in accordance with paragraph 7;

   h. Ensuring that the donation, selection and acceptance or rejection of tissues and cells intended for human application and

associated documentation are carried out in compliance with the parent directive and Commission Directive 2006/17/EC;

i. Ensuring that the processing, storage, labelling, packaging and distribution of tissues and cells intended for human application are carried out in compliance with the parent directive and Commission Directive 2006/17/EC; and

j. Ensuring that the establishment has written agreements with third parties on every occasion that an external activity takes place which influences the quality and safety of tissues and cells in accordance with paragraph 68.

5. Where the DI is unable to carry out their duties, whether permanently or temporarily, (e.g. where the DI is suspended pending investigation or is on extended sick leave) the Licence Holder shall immediately apply to the HTA for a licence variation to nominate a substitute DI. This nominated substitute DI shall not commence their post unless and until the HTA decides that they are suitable.

6. Tissue and cell procurement and testing shall be carried out by persons with appropriate training and experience and the laboratory tests required for donors in accordance with paragraph 25(f) shall be carried out by a laboratory with which the establishment has an appropriate Service Level Agreement (hereafter 'SLA').

Personnel

7. Personnel directly involved in activities relating to the procurement, processing, preservation, storage and distribution of tissues and cells shall, where appropriate, be registered in accordance with the appropriate professional and / or statutory bodies, (e.g. General Medical Council, Health Professions Council). The DI shall ensure that such personnel are provided with training in quality management and have the necessary competences to undertake such tasks as are assigned to them.

8. The DI shall ensure that at all times there are sufficient numbers of qualified staff to ensure that the requirements of the parent directive and Commission Directive 2006/17/EC are satisfied.

Licensing

9. The establishment shall carry out all appropriate control measures, at the establishment, at regular intervals, including but not limited to, control measures for the procurement of human tissues and cells intended for human application, to ensure compliance with the requirements of the parent directive and Commission Directive

2006/17/EC.

10. The HTA is regulating those establishments that do not store material but are involved in the donation, procurement, testing, processing, preservation and distribution of tissues and cells via the HT Act, 2004 by:

    a. requiring DI under a storage licence issued by the HTA to ensure that suitable practices are used in the carrying on of the licensed activity;

    b. requiring the DI to ensure that the conditions of the licence are complied with; and

    c. requiring the Designated Individual to ensure that appropriate SLAs are in place governing relations between the establishment and third parties including parties involved in the donation, procurement, testing, processing, preservation and distribution of tissues and cells and that appropriate Standard Operating Procedures (SOPs) are in place and complied with.

Consent

11. The establishment shall comply with the HTA's Codes of Practice, particularly the Code of Practice on consent (hereafter "the HTA Consent Code"), the Code of Practice on Donation of Organs, Tissue and Cells for Transplantation (hereafter "the HTA Donation Code") and the Code of Practice on Donation of Allogeneic Bone Marrow and Peripheral Blood Stem Cells for Transplantation (hereafter "the HTA BM Donation Code"). The establishment shall not procure any human tissues and cells unless and until they have satisfied themselves that the necessary consent has been properly obtained.

12. Prior to the procurement of tissues and cells, an authorised person from the procuring establishment must confirm and record:

    (a) that consent for the procurement has been obtained in accordance with the HT Act and the HTA Consent Code; and

    (b) how and by whom the donor has been reliably identified.

13. The establishment shall ensure that all necessary information which is required to be given to a prospective donor, or an individual or individuals giving consent on behalf of a donor, prior to the donation of human tissues and cells is provided in accordance with the provisions of the HTA Consent and Donation Codes.

14. In accordance with the requirements of the parent Directive, as a minimum, the establishment shall ensure that:

    a. Information is given by trained personnel in a manner and using terms that are easily understood by the prospective donor.

    b. The information to be provided prior to the donation of human tissues and / or cells must cover at least the purpose and nature of the donation, its consequence and risks, any analytical tests if they are to be performed, the recording and protection of donor data and medical confidentiality, therapeutic purpose and potential benefits of the donation, and information on the applicable safeguards intended to protect the prospective donor.

    c. The prospective donor must be informed that he / she has the right to receive the confirmed results of the analytical tests and in a manner and using terms that are easily understood by the donor.

    d. The prospective donor must be informed of the necessity for obtaining his / her prior consent in order that the procurement of the human tissues and / or cells is carried out.

    e. In addition, in the case of deceased donors, the confirmed results of the donor's evaluation (selection / assessment and testing) must be communicated and clearly explained to the individual or individuals giving consent on behalf of the deceased donor.

15. In addition, in the case of living donors, the healthcare professional responsible for obtaining the medical history or the Accredited Assessor must ensure that the donor has:

    (i) understood the information provided;

    (ii) had an opportunity to ask questions and been provided with satisfactory responses;

    (iii) confirmed that all the information provided is true to the best of his / her knowledge.

    The establishment must satisfy itself, whether directly or indirectly through SLAs and / or SOPs as appropriate that this provision has been fulfilled.

Data Protection and confidentiality

16. The establishment shall have SOPs to ensure that all information provided in confidence is kept confidential and only disclosed in circumstances permitted by law.

17. The establishment shall ensure that all data including genetic information collated for any purpose, and to which third parties have access, is rendered anonymous so that neither donors nor recipients remain identifiable.

18. The establishment shall ensure that the identity of the recipient is not disclosed to the donor or his / her relatives and vice versa, unless the donor and / or recipient have consented to such disclosure.

19. The establishment shall have in place an SOP for the control of access to health data and records, including arrangements for:

    a. Establishing and maintaining data security measures and safeguards against any unauthorised data additions, deletions or modifications to donor files or records, and the transfer of information.

    b. Establishing and maintaining procedures to resolve all data discrepancies.

    c. Preventing unauthorised disclosure of information whilst guaranteeing the traceability of donations.

    d. Considering and responding to applications for access to confidential records and correctly identifying applicants.

    e. Receiving, checking and arranging authorised access to confidential data and records.

    f. Notifying the Data Protection Commissioner in accordance with the Data Protection Act, 1988.

    g. Ensuring that data subjects are aware of their rights under the Data Protection Act, 1988 to access their own health records and correct information held about themselves.

Quality management

20. The establishment shall put in place a quality management system and continually improve its effectiveness in accordance with the requirements of these directions, as amended from time to time, and the principles of good practice.

21. The quality management system maintained by the establishment shall include at least the following documentation:

    a. A quality manual

    b. SOPs required by these directions

    c. Guidelines

    d. Training and Reference Manuals

    e. Reporting forms

    f. Donor Records and any records required by the HTA including those required by these directions

    g. Information on the final destination of human tissues and / or cells.

22. The establishment shall ensure that all documentation is available for inspection by a HTA duly authorised person or persons.

23. The establishment shall put in place an SOP to control all records required to provide evidence of conformity to these directions, to the effective operation of the quality management system, and to the conduct of the licensed activity. The SOP shall include the identification, collection, indexing, access, storage, maintenance, confidentiality and safe disposal of records.

24. Records shall be kept for a minimum period of thirty years after clinical use or disposal. The records referred to in paragraphs 21 and 23 above shall include the data necessary to ensure that all tissues and cells, procured, processed, stored and / or distributed by the establishment can be traced from the donor to the recipient and vice versa. This traceability shall also apply to all relevant data relating to products and materials coming into contact with such tissues and cells.

Donor selection and evaluation

25. In the selection and evaluation of potential donors, the establishment shall comply with the HTA Donation Code and shall in particular ensure that:

    a. Donations are voluntary and unpaid, and that compensation is restricted to expenses and inconveniences related to the donation.

b. The procurement of human tissues and cells as such is carried out on a non-profit basis. This is subject to the Act which allows the Licence Holder in certain circumstances to receive payment for the transportation, removal, preparation, preservation or storage of certain tissue and cells for transplantation provided that the terms of the Licence Holder's licence does not expressly prohibit such payment.

c. The prospective donor or individual or individuals granting consent on behalf of the prospective donor has received all the information required by the HTA Donation Code, the parent directive and Commission Directive 2006/17/EC.

d. No pressure, coercion or undue influence is or has been applied to the prospective donor or individual or individuals granting consent on his / her behalf, whether directly or indirectly.

e. All appropriate screening tests and the selection criteria as set out in Annex A to these directions have been performed, complied with and are recorded.

f. Donors of tissues and cells, except donors of reproductive cells, undergo the biological tests set out in, and in compliance with the requirements of, Annex B to these directions.

g. The results of the donor evaluation and testing procedures shall be documented and any major anomalies reported in accordance with paragraph 14 above.

h. Other than in the case of autologous donors:

(i) An authorised person must collect and record the donor's relevant medical and behavioural information. The complete donor records must be reviewed and assessed for suitability and signed by a qualified health professional.

(ii) In order to acquire the appropriate information, different relevant sources must be used, including at least an interview with the donor, for living donors, and the following when appropriate:

(a) the donor's medical records;

(b) an interview with the deceased's nominated representative, if applicable, or a person in a qualifying relationship;

(c) an interview with the treating physician;

(d) an interview with the general practitioner;

(e) the autopsy report; and

i. In addition, in the case of a deceased donor, and in the case of a living donor when justified, a physical examination of the body must be performed to detect any signs that may exclude the donor or which must be assessed in the light of the donor's medical and personal history.

Where the establishment is not directly involved in the selection and evaluation process, it shall have written agreements with the organisations, staff or clinical teams responsible for donor selection and evaluation (unless they are employed by the same establishment), specifying the procedures to be followed to ensure compliance with this paragraph.

Procurement and distribution (including packaging and transportation) of human tissues and cells

26. The procurement of human tissues and cells shall be carried out by personnel who have successfully completed a training programme as agreed with the Designated Individual. The competence of the trained personnel shall be recorded and retained.

27. The establishment shall have written agreements with the staff or clinical teams responsible for donor selection and tissue / cell procurement, unless they are employed by the same establishment, specifying the procedures to be followed to ensure compliance with the selection criteria set out in Annex A and specifying the types of tissues and / or cells, and / or test samples, to be procured and the protocols to be followed.

28. The establishment shall put in place and maintain SOPs for donation and procurement, packaging, labelling, transportation, distribution, and receipt of human tissues and cells that ensure:

a. That the required information has been provided in accordance with paragraphs 13 and 14 above;

b. Consent and donor identification;

c. Donor evaluation and assessment;

d. Procurement procedures for human tissues and cells including the safety of the living donor;

e. Donor documentation;

f. Packaging and distribution;

g. Labelling of packages containing procured tissues and cells;

h. Transportation and labelling of shipping containers transporting human tissues and cells meet the requirements of these directions and Commission Directive 2006/17/EC;

i. The quality and safety of human tissues and cells and minimisation of the risk of microbiological contamination;

j. That any serious adverse reaction or event that might result in harm to the donor is recorded and reviewed in accordance with paragraph 60 below;

k. Documentation of the results of the donor evaluation and testing procedures and the reporting of any major anomalies.

29. The procedures for tissue and / or cell donation and procurement and the reception of tissues and / or cells at the establishment including the management of procurement materials and equipment shall comply with the following:

(a) Procurement procedures must be appropriate for the type of donor and the type of tissue / cells donated. There must be procedures in place at all times to protect the safety of the living donor.

(b) Procurement procedures must protect those properties of the tissue / cells that are required for their ultimate clinical use, and at the same time minimise the risk of microbiological contamination during the process, particularly when tissues and cells cannot subsequently be sterilised.

(c) For deceased donation, the area of access must be restricted. A local sterile field using sterile drapes must be used. Personnel conducting procurement must be clothed appropriately and this will usually extend to being scrubbed, gowned in sterile clothing and wearing sterile gloves, face shields and protective masks.

(d) In the case of a deceased donor, the place of procurement must be recorded and the time interval from death to procurement must be specified to ensure that the required biological and / or physical properties of the tissues / cells are retained.

(e) Once the tissues and cells have been retrieved from a deceased donor body, it must be reconstructed so that it is as similar as possible to its original anatomical appearance.

(f) Any adverse event occurring during procurement that has or may have resulted in harm to a living donor and the outcome of any investigation to determine the cause must be recorded and reviewed.

(g) Policies and procedures must be in place to minimise the risk of tissue or cell contamination by personnel who might be infected with transmissible diseases.

(h) Sterile instruments and devices must be used for tissue and cell procurement. Instruments or devices must be of good quality, validated or specifically certified and regularly maintained for the procurement of tissues and cells.

(i) When use of reusable instruments is necessary, a validated cleaning and sterilisation procedure for removal of infectious agents has to be in place.

(j) Wherever possible, only CE marked medical devices must be used and all concerned personnel must have received appropriate training on the use of such devices.

30. Tissue and / or cell procurement shall take place in facilities which are appropriate and fit for purpose and following procedures that minimise bacterial or other contamination. Qualified sterile instruments and procurement devices shall be used at all times for tissue and / or cell procurement.

31. Procurement of tissues and cells from living donors shall take place in conditions ensuring their health, safety and privacy.

32. Procurement of tissues and cells from deceased donors shall take place in conditions ensuring that respect and dignity are accorded to the deceased donor at all times and trained staff and equipment necessary for effective body reconstruction shall be provided by the procuring establishment.

The SOPs established and maintained in accordance with paragraphs 28 and 29 above shall also include the procedures necessary to ensure compliance with paragraphs 30, 31 and this paragraph.

Donor documentation

33. For each donor, the establishment must maintain a record containing:

    a. donor identification: first name, family name, date of birth, age and sex;

    b. medical and behavioural history;

    c. outcome of body examination, where applicable;

    d. haemodilution formula, where applicable;

    e. consent, including the purpose or purposes for which the human tissues and cells may be used, and any specific instructions for use and / or disposal. This may be the consent form or evidence of consent, where applicable;

    f. clinical and laboratory assessment data including the results of any tests carried out;

    g. the results of any autopsy performed, (for tissues and cells that cannot be stored for extended periods, the recording of a preliminary verbal report);

    h. for haematopoietic progenitor cell donors, documented evidence of the donor's suitability for the chosen recipient. In the case of unrelated donations, when the establishment responsible for procurement has limited access to recipient data, the transplanting establishment must be provided with donor data relevant for confirming suitability; and

    i. where a mother and child are involved in the donation, the name (if known) and date of birth of the child and also the name and date of birth of the mother.

34. Where human tissues and / or cells have been procured by a third party on behalf of a licensed establishment, there must be a contract or SLA requiring the procuring establishment to produce a report to the establishment which shall include, but not be limited to, the following:

    a. the identification, name and address of the establishment to receive the tissues and / or cells;

    b. donor identification data including how and by whom identified;

    c. description and identification of procured tissues and / or cells including samples for testing;

d. identification of the person responsible for the procurement process;

e. date, time and location of procurement and SOP used;

f. details of any incidents, including any serious adverse events and / or reactions, that occurred during the procurement process;

g. where appropriate, environmental conditions at the procurement facility;

h. for deceased donors, conditions under which the body was kept, including whether refrigerated or not and the start and end time of refrigeration;

i. where appropriate, the identification / batch numbers for any re-agents and transport media used;

j. date and time of death, where appropriate and where possible.

35. All records must be clear and readable, protected from unauthorised amendment and retained and readily retrieved in this condition throughout their specified retention period in compliance with data protection legislation.

36. Donor records required for full traceability must be kept for a minimum of 30 years after clinical use, or the expiry date, in an appropriate archive.

Packaging and distribution

37. Following procurement, all tissues and cells shall be packaged in a manner and under conditions that minimise the risk of contamination and ensures their safety and quality. This means that tissues and cells must be stored at the optimal temperature required to preserve their characteristics and biological function. The packaging used must also prevent contamination of individuals packaging and transporting the tissue and cells.

38. The packaged tissues and / or cells must be shipped in a container which, is suitable for the transport of biological material, maintains the safety and quality of the tissue and / or cells, and complies with all relevant national legislation and regulations.

39. Any accompanying tissue or blood samples for testing must be accurately labelled to ensure identification with the donor, and must include a record of the time and place the specimen was taken.

Labelling of procured tissues and / or cells

40. At the time of procurement, every package containing tissues and / or cells must be accurately labelled. Primary containers must indicate the donor identification or code and the type of tissues and cells. Where the size of the package permits, the following information must also be provided:-

    a. date (and time where possible) of donation;

    b. hazard warnings;

    c. nature of any additives, if used;

    d. in the case of autologous donations, the label must state: “for autologous use only”; and

    e. in the case of directed donations, the label must state the identity of the intended recipient.

    If any of the above information cannot be included on the primary package label, it must be provided on a separate sheet accompanying the primary package.

Transportation, labelling of shipping container and recall

41. The transportation of tissues and / or cells shall be carried out in a manner and under conditions that ensure their safety and quality at all times. When tissues and / or cells are transported by a third party, the third party shall be subject to a third party contract, in accordance with paragraph 68 and a documented agreement to ensure that the required conditions are fulfilled.

    The transport conditions, including temperature and time limit, shall be specified and the labelling of every shipping container must include a minimum of:

    a. Label marked “TISSUES AND CELLS” and “HANDLE WITH CARE”.

    b. The identification of the establishment from which the package is being transported (address and telephone number), and the name of a contact person in the event of problems.

    c. The identification of the establishment to which the package is to be delivered (address and telephone number) and contact person to accept delivery.

d. The date and time of the start of transportation.

e. Specifications concerning the conditions of transport relative to the quality and safety of the tissues and / or cells.

f. Specifications concerning storage conditions such as DO NOT FREEZE.

g. In the case of all cellular products, a label with DO NOT IRRADIATE.

h. In the case of autologous donors, a label marked FOR AUTOLOGOUS USE ONLY.

i. When a product is known to be positive for a relevant infectious disease marker, a label marked BIOLOGICAL HAZARD.

42. The establishment from which the tissues and /or cells originated shall have a recall procedure that defines the responsibilities and actions required when a distribution is recalled. Such a recall would be investigated in accordance with paragraph 60. The establishment from which the tissues and / or cells originated shall also have a procedure for handling returned tissues and / or cells.

Receipt of tissues and / or cells

43. The establishment shall put in place and maintain a procedure for the receipt of tissues and / or cells from another establishment to ensure that:

a. Consignment of tissues / and or cells are verified against SOPs and specifications. These shall include the requirements for transport, packaging, labelling, including labelling for shipping containers, donor documentation, and any other associated documentation and samples. These must also include the technical requirements and other criteria considered by the establishment to be essential for the maintenance of acceptable quality.

b. Pending verification that the tissues and / or cells and associated documentation conform to the requirements of these directions, the parent directive and Commission Directive 2006/17/EC, the tissue and / or cells are quarantined. The review of relevant donor / procurement information and thus acceptance of the donation needs to be carried out by authorised persons.

c. Verification is undertaken only by authorised personnel.

d. SOPs for the management and segregation of non-conforming consignments or those with incomplete test results to ensure no risk of contamination of either tissues and / or cells being processed, preserved or stored.

e. Records are maintained to demonstrate that before tissues and / or cells are released, all appropriate specifications have been met.

f. Quarantined consignments are not released until (c) and (e) above are satisfied; and

44. The establishment must register the following data:

a. Consent including the purpose for which tissues and cells may be used (i.e. therapeutic or research, or both therapeutic and research) and any specific instructions for disposal, if not used for the consented purpose.

b. All required records relating to the procurement and the taking of the donor history, as described in paragraphs 33–36 above;

c. The results of physical examination, of laboratory tests, and other tests, including autopsy report, if used in accordance with paragraph 25(h)(ii) above;

d. For allogenic donors, a documented review of the complete donor evaluation against the selection criteria carried out by authorised and trained personnel;

e. In the case of cell cultures intended for autologous use, documentation of the possibility of medicinal allergies (such as to antibiotics) of the recipient.

45. The establishment shall verify and record that the packaging of human tissue and cells received complies with the required specifications and requirements and shall discard all tissues and cells that do not comply with such specifications and requirements.

46. The establishment shall document the acceptance or rejection of received tissues and / or cells.

47. The establishment shall ensure that human tissues and cells are correctly identified at all times and that each delivery of tissues or cells is assigned an identifying code in accordance with paragraph 54.

Tissue and cell processing and storage

48. The establishment shall have SOPs covering all processes that affect quality and safety and the storage of tissues and / or cells, including any modification of any such process.

49. The establishment shall ensure that all processing and storage are carried out under controlled conditions.

50. The establishment shall include in their SOPs special provisions for the handling of tissues and cells to be disposed of to prevent contamination of other tissues and / or cells, the processing environment or personnel.

51. The establishment shall maintain and apply procedures for the control of packaging and storage areas to prevent the functioning or integrity of tissues and or / cells being adversely affected.

52. The establishment shall not distribute any processed tissues or cells until satisfied that the requirements of these directions and the parent directive have been satisfied.

53. The establishment must have an SOP and / or agreement to ensure that in the event of termination of activities for whatever reason, stored tissues and / or cells are transferred to another licensed establishment or establishments.

Traceability and Coding

54. The establishment shall have SOPs to ensure that all tissues and / or cells procured, processed, stored or distributed are traceable from donor to recipient and vice versa, and shall ensure:

    a. The unique and accurate identification of each donor, donation and any and all products associated with the donation.

    b. The labelling of packages and containers containing tissues and cells received and distributed.

    c. That all relevant data relating to products and materials coming into contact with tissues and / or cells received and distributed is traceable from donor to recipient, and vice versa.

55. The establishment shall keep data necessary to ensure traceability at all stages for a minimum of thirty years after clinical use or expiry as the case may be.

56. The establishment shall use an identifying code to ensure the traceability of all tissues and / or cells and released data. The HTA will issue further guidance when the requirement for a European identifying code specified in the parent directive is clarified by the European Commission.

Register and reporting

57. The establishment shall keep the following registers:

    a. A register of the types and quantities of tissues and / or cells, procured, tested, preserved, processed, stored and distributed or otherwise disposed of, and on the origin and destination of tissues and cells intended for human applications.

    b. A register of the coded data assigned to each donor and donation of tissues and cells in accordance with paragraph 54 above.

58. The establishment shall submit to the HTA an annual report of their activities including the information referred to in paragraph 57 (a) above.

59. The HTA shall maintain a publicly accessible register of establishments specifying the activities for which they have been licensed.

Identification, investigation, reporting, recording and notification of serious adverse events and reactions

60. The establishment shall have an SOP for the identification, investigation, reporting, recording and notification of serious adverse events and reactions, that ensure that:

    a. The responsibilities of personnel responsible for the management of serious adverse events and reactions are clearly defined.

    b. The identification and investigation of serious adverse events and reactions including identification through risk assessment and internal audit.

    c. The recording of serious adverse events and reactions including an analysis of their cause, the corrective action taken and ensuing outcome.

d. The cessation of tissue and / or cell processing where required.

e. The identification of any individual who might have contributed to the serious adverse event or reaction.

f. The control and verifiable recall of any tissues and / or cells distributed which may be related to any particular adverse event or reaction, within a pre-defined time.

g. The control and verifiable recall of any tissues and / or cells, and the investigation of any equipment used in association with the adverse event and reaction.

h. The retention of all records in association with the serious adverse events and reactions.

i. The reporting of relevant information to personnel within the establishment and to other establishments engaged in the donation, procurement, testing, processing, storage and distribution of human tissues and cells in order to facilitate traceability and ensure safety and quality controls; and

j. Notification by the DI to the HTA of any serious adverse event or reaction and the provision of a report analysing the cause and ensuing outcome.

61. Serious adverse events and reactions are defined in Annex C. The notification and reporting of serious adverse events and reactions, including the furnishing of conclusion and confirmation reports, shall be notified to establishments by way of supplemental directions following publication of the EU Commission's Second Technical Directive.

62. The DI must notify the HTA of any serious adverse event or serious adverse reaction as soon as possible after the incident and must provide to the HTA a report analysing the cause and ensuing outcome. Following notification of any serious adverse event or serious adverse reaction, the HTA shall, at its discretion, organise an inspection of the establishment and shall require the establishment to carry out such control measures as are deemed appropriate in all the circumstances.

63. The HTA may also carry out an inspection and require control measures to be carried out at the request of a competent authority in another member state of the EU.

Import, export and distribution of human tissues and cells

64. Establishments that import human tissues and cells from third countries shall take all necessary measures to ensure: -

a. That such imports are undertaken by establishments licensed for that purpose;

b. That imported tissues and cells can be traced from the donor to the recipient and vice versa in accordance with paragraph 53;

c. That such imports meet the standards of quality and safety set out in these directions and the parent directive.

65. Establishments that export human tissues and cells to third countries shall ensure that such exports comply with these directions and the parent directive.

66. The establishment shall keep a complete list of agreements established with third parties in accordance with paragraph 68 below.

67. The establishment shall ensure the quality of human tissues and / or cells during distribution.

Tissue Establishments and Third Party Relations

68. The establishment shall put in place and maintain written agreements with third parties whenever an activity takes place which has the potential to influence the quality and safety of human tissues and cells processed, and in particular where:

a. The establishment entrusts one of the stages of tissue or cell processing to a third party.

b. A third party provides goods or services that affect tissue or cell quality and safety assurance, including their distribution;

c. The establishment provides services to a non-licensed establishment; or

d. The establishment distributes tissues and / or cells processed by third parties.

69. The establishment shall evaluate and select third parties on the basis of their ability to meet the requirements of these directions and the parent directive.

70. The establishment shall keep a complete list of agreements established with third parties, including third parties from third countries (i.e. countries outside the EU), and such agreements shall specify the responsibilities of the third parties and any and all agreed procedures. Copies of these agreements shall be made available to the HTA on request.

71. Agreements between the establishment and third parties shall be examined within the context of the establishment's licensed activity or activities, and the conditions of any licence granted to the establishment by the HTA.

Miscellaneous

72. These directions are made by the HTA.

Dated: 25 April 2006

Signed 

Adrian McNeil
Chief Executive
Human Tissue Authority

Annex A

Annex I Commission Directive 2006/17/EC

SELECTION CRITERIA FOR DONORS OF TISSUES AND/OR CELLS (EXCEPT DONORS OF REPRODUCTIVE CELLS) AS REFERRED TO IN ARTICLE 3(a)

Selection criteria for donors are based on an analysis of the risks related to the application of the specific cells/tissues. Indicators of these risks must be identified by physical examination, review of the medical and behavioural history, biological testing, post-mortem examination (for deceased donors) and any other appropriate investigation. Unless justified on the basis of a documented risk assessment approved by the responsible person as defined in Article 17 of Directive 2004/23/EC, donors must be excluded from donation if any of the following criteria applies:

1. Deceased Donors

1.1. *General criteria for exclusion*

1.1.1. Cause of death unknown, unless autopsy provides information on the cause of death after procurement and none of the general criteria for exclusion set out in the present section applies.

1.1.2. History of a disease of unknown aetiology.

1.1.3. 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 scientific evidence. Donors with malignant diseases can be evaluated and considered for cornea donation, except for those with retinoblastoma, haematological neoplasm, and malignant tumours of the anterior segment of the eye.

1.1.4. Risk of transmission of diseases caused by prions. This risk applies, for example, to:

(a) people diagnosed with Creutzfeldt–Jakob disease, or variant Creutzfeldt-Jacob disease, or having a family history of non-iatrogenic Creutzfeldt-Jakob disease;

(b) people with a history of rapid progressive dementia or degenerative neurological disease, including those of unknown origin;

(c) recipients of hormones derived from the human pituitary gland (such as growth hormones) and recipients of grafts of cornea, sclera and dura mater, and persons that have undergone undocumented neurosurgery (where dura mater may have been used).

For variant Creutzfeldt-Jakob disease, further precautionary measures may be recommended.

1.1.5. Systemic infection which is not controlled at the time of donation, including bacterial diseases, systemic viral, fungal or parasitic infections, or significant local infection in the tissues and cells to be donated. Donors with bacterial septicaemia may be evaluated and considered for eye donation but only where the corneas are to be stored by organ culture to allow detection of any bacterial contamination of the tissue.

1.1.6. History, clinical evidence, or laboratory evidence of HIV, acute or chronic hepatitis B (except in the case of persons with a proven immune status), hepatitis C and HTLV I/II, transmission risk or evidence of risk factors for these infections.

1.1.7. History of chronic, systemic autoimmune disease that could have a detrimental effect on the quality of the tissue to be retrieved.

1.1.8. Indications that test results of donor blood samples will be invalid due to:

(a) the occurrence of haemodilution, according to the specifications in Annex II, section 2, where a pre-transfusion sample is not available; or

(b) treatment with immunosuppressive agents.

1.1.9. Evidence of any other risk factors for transmissible diseases on the basis of a risk assessment, taking into consideration donor travel and exposure history and local infectious disease prevalence.

1.1.10. Presence on the donor’s body of physical signs implying a risk of transmissible disease(s) as described in Annex IV, point 1.2.3.

1.1.11. Ingestion of, or exposure to, a substance (such as cyanide, lead, mercury, gold) that may be transmitted to recipients in a dose that could endanger their health.

1.1.12. Recent history of vaccination with a live attenuated virus where a risk of transmission is considered to exist.

1.1.13. Transplantation with xenografts.

1.2. *Additional exclusion criteria for deceased child donors*

1.2.1. Any children born from mothers with HIV infection or that meet any of the exclusion criteria described in section 1.1 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, hepatitis C or HTLV infection, or at risk of such infection, and 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 of mothers with HIV, hepatitis B, hepatitis C or HTLV infection, or at risk of such infection, and 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, hepatitis C or HTLV infection, can be accepted as donors.

2. Living donors

2.1. *Autologous living donor*

2.1.1. If the removed tissues and cells are to be stored or cultured, the same minimum set of biological testing requirements must apply as for an allogeneic living donor. Positive test results will not necessarily prevent the tissues or cells or any product derived from them being stored, processed and reimplanted, if appropriate isolated storage facilities are available to ensure no risk of cross-contamination with other grafts and / or no risk of contamination with adventitious agents and/or mix-ups.

2.2. *Allogeneic living donor*

2.2.1. Allogeneic living donors must be selected on the basis of their health and medical history, provided on a questionnaire and through an interview performed by a qualified and trained healthcare professional with the donor, in compliance with point 2.2.2. This assessment must include relevant factors that may assist in identifying and screening out persons whose donation could present a health risk to others, such as the possibility of transmitting diseases or health risks to themselves. For any donation, the collection process must not interfere with or compromise the health or care of the donor. In the case of cord blood or amniotic membrane donation, this applies to both mother and baby.

2.2.2. Selection criteria for allogeneic living donors must be established and documented by the tissue establishment (and the transplanting clinician in the case of direct distribution to the recipient), based on the specific tissue or cells to be donated, together with the donor’s physical status and medical and behavioural history and the results of clinical investigations and laboratory tests establishing the donor’s state of health.

2.2.3. The same exclusion criteria must be applied as for deceased donors with the exception of point 1.1.1. Depending on the tissue or cell to be donated, other specific exclusion criteria may need to be added, such as:

(a) pregnancy (except for donors of umbilical cord blood cells and amniotic membrane and sibling donors of haematopoietic progenitors);

(b) breastfeeding;

(c) in the case of haematopoietic progenitor cells, the potential for transmission of inherited conditions.

Annex B

Annex II of Commission Directive 2006/17/EC

Laboratory tests required for donors (except donors of reproductive cells) as referred to in article 4(1)

1. Biological tests required for donors

1.1. The following biological tests must be performed for all donors as a minimum requirement:

HIV 1 and 2	Anti-HIV-1,2
Hepatitis B	HBsAg Anti HBc
Hepatitis C	Anti-HCV-Ab
Syphilis	See 1.4 (below)

1.2. HTLV-I antibody testing must be performed for donors living in, or originating from, high-incidence areas or with sexual partners originating from those areas or where the donor's parents originate from those areas.

1.3. When anti-HBc is positive and HBsAg is negative, further investigations are necessary with a risk assessment to determine eligibility for clinical use.

1.4. A validated testing algorithm must be applied to exclude the presence of active infection with *Treponema pallidum*. A non-reactive test, specific or non-specific, can allow tissues and cells to be released. When a non-specific test is performed, a reactive result will not prevent procurement or release if a specific Treponema confirmatory test is non-reactive. A donor whose specimen tests reactive on a Treponema-specific test will require a thorough risk assessment to determine eligibility for clinical use.

1.5. In certain circumstances, additional testing may be required depending on the donor's history and the characteristics of the tissue or cells donated (e.g. RhD, HLA, malaria, CMV, toxoplasma, EBV, *Trypanosoma cruzi*).

1.6. For autologous donors, Annex I, point 2.1.1, applies.

2. General requirements to be met for determining biological markers

2.1. The tests must be carried out by a qualified laboratory, authorised as a testing centre by the competent authority in the Member State, using EC-marked testing kits where appropriate. The type of test used must be validated for the purpose in accordance with current scientific knowledge.

2.2. The biological tests will be carried out on the donor's serum or plasma; they must not be performed on other fluids or secretions such as the aqueous or vitreous humour unless specifically justified clinically using a validated test for such a fluid.

2.3. When potential donors have lost blood and have recently received donated blood, blood components, colloids or crystalloids, blood testing may not be valid due to haemodilution of the sample. An algorithm must be applied to assess the degree of haemodilution in the following circumstances:

(a) ante-mortem blood sampling: if blood, blood components and/or colloids were infused in the 48 hours preceding blood sampling or if crystalloids were infused in the hour preceding blood sampling;

(b) post mortem blood sampling: if blood, blood components and/or colloids were infused in the 48 hours preceding death or if crystalloids were infused in the hour preceding death.

Tissue establishments may accept tissues and cells from donors with plasma dilution of more than 50 % only if the testing procedures used are validated for such plasma or if a pre-transfusion sample is available.

2.4. In the case of a deceased donor, blood samples must have been obtained just prior to death or, if not possible, the time of sampling must be as soon as possible after death and in any case within 24 hours after death.

2.5. (a) In the case of living donors (except allogeneic bone marrow stem-cell and peripheral blood stem-cell donors, for practical reasons), blood samples must be obtained at the time of donation or, if not possible, within seven days post donation (this is the 'donation sample').

(b) Where tissues and cells of allogeneic living donors can be stored for long periods, repeat sampling and testing is required after an interval of 180 days. In these circumstances of repeat testing, the donation sample can be taken up to 30 days prior to and 7 days post donation.

(c) Where tissues and cells of allogeneic living donors cannot be stored for long periods and repeat sampling is therefore not possible, point 2(5)(a) above applies.

2.6. If in a living donor (except bone marrow stem-cell and peripheral blood stem-cell donors) the 'donation sample', as defined in point 2(5)(a) above, is additionally tested by the nucleic acid amplification technique (NAT) for HIV, HBV and HCV, testing of a repeat blood sample is not required. Retesting is also not required if the processing includes an inactivation step that has been validated for the viruses concerned.

2.7. In the case of bone marrow and peripheral blood stem-cell collection, blood samples must be taken for testing within 30 days prior to donation.

2.8. In the case of neonatal donors, the biological tests may be carried out on the donor’s mother to avoid medically unnecessary procedures upon the infant.

Annex C

Definitions

Terms used in these directions bear the same meaning as set out in the HTA's Codes of Practice, unless otherwise stated.

Cells: means individual human cells or a collection of human cells when not bound by any form of connective tissue.

Tissue: means all constituent parts of the human body formed by cells.

Procurement*:* means a process by which tissues or cells are made available.

Processing: means all operations involved in the preparation, manipulation, preservation and packaging of tissues or cells intended for human applications.

Preservation: means the use of chemical agents, alterations in environmental conditions or other means during processing to prevent a retard biological or physical deterioration of cells or tissues.

Quarantine: means the status of retrieved tissue or cells, or tissue isolated physically or by other effective means, whilst awaiting a decision on their acceptance or rejection.

Distribution: means transportation and delivery of tissues or cells intended for human applications.

Human application: means the use of human tissues or cells on or in a human recipient and extracorporal applications.

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, hospitalization or morbidity.

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.