

Directions given under the Human Tissue Act 2004 implementing the Human Tissue (Quality and Safety for Human Application) Regulations 2007

Directions on the requirements of the Human Tissue (Quality and Safety for Human Application) Regulations 2007, and in particular Regulation 15 relating to the import and export of tissues and / or cells for human application.

Ref 004/2007

These Directions are

Given in relation to licences to store tissues and / or cells for human application under Regulation 7(1) of the Human Tissue (Quality and Safety for Human Application) Regulations 2007 and Licences and / or third party agreements for the procurement, testing, processing, distribution, import or export of tissues and / or cells for human application under Regulation 7(2) of the Regulations.

<p>Section of the Human Tissue Act 2004 (HT Act) and Regulation under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (the Regulations) providing for these Directions</p>	<p>Section 23 (1) of the HT Act and Regulation 15 of the Regulations</p>
<p>These Directions come into force on</p>	<p>7 October 2007</p>
<p>These Directions remain in force</p>	<p>Until revoked</p>

General

1. These Directions are made for the purposes of securing compliance with the requirements of 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”), 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 “the First Commission Directive”) and Commission Directive 2006/86/EC of 24 October 2006 setting out the traceability requirements, requirements for the notification of serious adverse reactions and events and specifying the technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells (hereafter “the Second Commission Directive”) in accordance with Regulation 15 (1) and (2) of the Regulations.
2. These Directions supplement the Directions given under the HT Act, reference number 001/2006 as amended, and Directions reference number 002/2007.
3. These Directions are made under section 23 (1) of the HT Act in order to comply with Regulation 15 (1) of the Regulations and to secure that all imports of tissues and / or cells intended for human application from countries which are not member states of the European Economic Area (“non – EEA member states”), meet standards of quality and safety equivalent to those provided for in the Regulations.
4. These Directions have regard to the need to ensure traceability of tissues and / or cells intended for human application in accordance with the obligations of the Human Tissue Authority (HTA) under Regulation 15 (2) of the Regulations.
5. For the purposes of the Regulations, and these Directions, Gibraltar is to be considered an EEA member state.
6. References to linking or linked paragraphs are included in these Directions to facilitate persons using these Directions and do not form part of the Directions.

Interpretation

7. The parent Directive, the First Commission Directive and the Second Commission Directive (hereafter collectively referred

to as “the Directives”) have been brought into UK law by way of the Regulations. Except as otherwise provided in **Annex B** of these Directions, words and expressions used in these Directions shall have the same meaning as in Article 3 of the parent Directive, Article 1 of the First Commission Directive, and Article 2 of the Second Commission Directive.

8. References in these Directions to “storage” means maintaining tissue or cells, whether by preservation or in any other way, for more than 48 hours. The words “store” and “storage” are to be interpreted accordingly.

HTA Code of Practice on Import and Export

9. The establishment shall comply with the HTA’s Code of Practice on import and export of human bodies, body parts and tissue (hereafter “the HTA Import / Export Code”) as appropriate.
10. The HTA Import / Export Code makes it clear that it is good practice to ensure that mechanisms are in place in the source country for obtaining consent and that importers should satisfy themselves that the obtaining of consent, for the purpose to which the tissues and / or cells are subsequently put, is part of the process within the source country by which the tissues and / or cells are obtained.

Tissue and cell procurement

11. Prior to the import of tissues and / or cells for human application from a country which is a non – EEA member state, the establishment shall satisfy itself, whether directly or indirectly through service level agreements (SLAs), and / or standard operating procedures (SOPs) with the establishment from the source country, or otherwise, that the following minimum provisions have been fulfilled: –
 - a. Information is given prior to the donation of human tissues and / or cells by trained personnel in a manner and using terms that are easily understood by the prospective donor, or individual or individuals giving consent on behalf of the donor as appropriate;
 - 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 consequences and risks, any analytical tests if they are to be performed, the recording and protection of donor data and medical confidentiality, therapeutic purposes and potential benefits of the donation, and information on the applicable

safeguards intended to protect the prospective donor;

- c. Where required by the source country, the prospective donor must be informed of the necessity for obtaining his / her prior consent or authorisation to the donation in order that the procurement of the human tissues and / or cells is carried out;
 - d. Where required by the source country, the prospective donor must be informed that he / she has the right to receive the confirmed results of any analytical tests carried out on the donor and in a manner and using terms that are easily understood by the donor;
 - e. In the case of deceased donors, and where required by the source country, 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;
 - f. The identity of the recipient shall not be disclosed to the donor or his / her relatives and vice versa, unless the donor and / or recipient have consented to such disclosure. This shall not preclude authorised personnel within the establishment from obtaining information identifying either the donor and / or the recipient, where necessary;
 - g. No pressure, coercion or undue influence has been applied to the prospective donor or individual or individuals giving consent on behalf of the donor, whether directly or indirectly;
 - h. How and by whom the donor has been reliably identified;
 - i. All appropriate screening tests have been performed, complied with and are recorded; and
 - j. In the selection and evaluation of potential donors, Donations should, in principle, be voluntary and unpaid, and the procurement of human tissues and / or cells as such should be carried out on a non-profit basis.
12. The establishment shall ensure that the biological tests set out in **Annex A** of these Directions are carried out in compliance with the requirements of Annex A, and on all tissues and / or cells imported from non – EEA member states.
13. The establishment shall satisfy itself, whether directly or indirectly through SLAs, and / or SOPs with the establishment from the source country, or otherwise, that the procedures for

tissues and / or cells procurement including the management of procurement materials and equipment comply with the following:

- a. Procurement procedures must be appropriate for the type of donor and the type of tissues and/or 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. 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; **[see serious adverse events / serious adverse reactions (SAE / SAR) [20] – [21]]**
- d. 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;
- e. Sterile instruments and devices must be used at all times for tissue and cell procurement;
- f. 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;
- g. Procurement of tissues and cells from living donors shall take place in conditions ensuring their health and safety; and
- h. 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.

Donor documentation

14. 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, where appropriate, behavioural history;

- c. Haemodilution formula, where applicable;
- d. Where required by the source country, consent or authorisation, 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 or authorisation, where applicable;
- e. Clinical and laboratory assessment data including the results of any tests carried out;
- f. The results of any autopsy performed;
- g. 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
- h. 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.

Tissue and cell processing

- 15. The establishment shall satisfy itself, whether directly or indirectly, through SLAs and / or SOPs with the establishment from the source country, or otherwise, that: –
 - a. Any critical processing procedures undertaken must not render the tissues and / or cells clinically ineffective or harmful to the recipient;
 - b. Procedures are maintained and applied within the establishment in the source country for the handling of the tissues and / or cells to be disposed of to prevent contamination of other tissues and / or cells, the processing environment or personnel involved in the processing of tissues and / or cells;
 - c. All processing is carried out under controlled conditions;
 - d. Procedures for discarding tissues and / or cells must prevent the contamination of other donations and products, the processing environment or personnel. These procedures must comply with national Regulations and guidelines, if any;

- e. An effective recall procedure is in place in the establishment within the source country which shall include the tracing of all relevant tissues and / or cells as appropriate. The purpose of the investigation is to identify any donor who might have contributed to causing the reaction in the recipient and to retrieve available tissues and / or cells from that donor, as well as to notify consignees and recipients of tissues and / or cells procured from the same donor in the event that they might have been put at risk; and **[see Import and Distribution [22] – [24]]**
- f. The risks inherent in the use and handling of biological material are identified and minimised, consistent with maintaining adequate quality and safety for the intended purpose of the tissues and / or cells. This includes risks relating in particular to the procedures, environment and staff health status specific to the establishment within the source country.

Packaging, labelling and transportation

- 16. The establishment shall satisfy itself, whether directly or indirectly, through SLAs and / or SOPs as appropriate with the establishment within the source country, or otherwise, that appropriate packaging, labelling, transportation (including storage) and distribution procedures are used and maintained at all times to secure the integrity, safety and quality of the imported tissues and / or cells.
- 17. The establishment shall ensure as a minimum that: –
 - a. The integrity, quality and safety of the tissues and / or cells is not compromised by the packaging, labelling, transportation and distribution of the tissues and / or cells and that the risk of microbiological contamination is minimal;
 - b. Every package containing tissues and / or cells must be accurately labelled to include the donor identification or code, the type of tissues and / or cells, hazard warnings where appropriate and the nature of any additives, if used;
 - c. The tissues and / or cells must be maintained at the optimal temperature required to preserve their characteristics and biological function;

- d. The tissues and / or cells are transported in a manner and under conditions that ensure their quality and safety at all times;
- e. The establishment from which the package is being transported and the establishment to which the package is to be delivered must be included on the labelling of any external or shipping container used to transport the tissues and / or cells;
- f. Recommended transport conditions, if any, and safety instructions are included on the external or shipping container to include any specifications in relation to transportation; and
- g. The establishment from which the tissues and / or cells originated has a recall procedure that defines the responsibilities and actions required when a distribution is recalled. **[see Import and Distribution [22] – [24]]**

Traceability

- 18. The establishment shall satisfy itself, whether directly or indirectly, through SLAs and / or SOPs as appropriate or other documented evidence with the establishment within the source country that tissues and / or cells procured, processed, stored, tested, distributed or imported are traceable from the donor to the recipient and vice versa.
- 19. The SLA, SOP or other written documentary evidence referred to in paragraph **[18]** above 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 / or cells imported;
 - c. That all relevant data relating to products and materials coming into contact with imported tissues and / or cells is traceable from the donor to the recipient, and vice versa; and
 - d. The establishment within the source country retains, as a minimum the following data for a period of at least 30 years:

- (i) Confirmation of when the tissues and/or cells were procured;
- (ii) Details of where the tissues and/or cells were procured from;
- (iii) Product identification including pool number or split number (if applicable);
- (iv) Description of any processing steps applied and materials and additives coming into contact with the tissues and / or cells and having an effect on their quality and / or safety;
- (v) The date the tissues and / or cells were transported; and
- (vi) To whom the tissues and / or cells were transported.

Identification, reporting, recording and notification of Serious Adverse Events and Serious Adverse Reactions

- 20. The establishment shall satisfy itself, whether directly or indirectly through SLAs and / or SOPs as appropriate, or otherwise, with the establishment within the source country that it is informed of any and all serious adverse events and / or serious adverse reactions affecting or having the ability to affect the imported tissues and / or cells.
- 21. The SLA, SOP or other system for the identification, reporting, recording and notification of serious adverse events and / or serious adverse reactions, referred to in paragraph **[20]** above, shall include: –
 - a. The identification of serious adverse events and / or serious adverse reactions by the establishment within the source country;
 - b. The recording of serious adverse events and / or serious adverse reactions including an analysis of their cause, the corrective action taken and ensuing outcome;
 - c. The recall of any tissues and / or cells which may be related to any particular serious adverse event or serious adverse reaction within a pre-defined time;
 - d. The retention of records in association with the serious adverse event and / or serious adverse reaction;

- e. The reporting of relevant information to the establishment in order to facilitate traceability and ensure safety and quality controls; and
- f. The evaluation of serious adverse events by the establishment within the source country to identify preventable causes within the process.

Import and distribution

- 22. Establishments that import human tissues and / or cells from countries which are non – EEA member states shall comply with paragraph 64 of Directions 001/2006 as amended by paragraph 108 of Directions 002/2007 and paragraphs 109 to 114 of Directions 002/2007 as appropriate.
- 23. The establishment shall ensure that imported tissues and / or cells can be traced from the donor to recipient and vice versa at all times. **[see traceability [18] – [19]]**
- 24. The establishment shall ensure that the establishment within the source country has an effective recall procedure in accordance with paragraph **[15 (e)]** above. **[see tissue and cell processing [15]]**

Miscellaneous

- 25. These Directions are made by the HTA.

Dated the 27 day of September 2007.

Signed:



Adrian McNeil
Chief Executive
Human Tissue Authority

Annex A

Laboratory tests required for all tissues and / or cells (except reproductive cells)

1. Biological tests required for all tissues and / or cells

1.1. The following biological tests must be performed for all tissues and/or cells 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 on tissues and / or cells from 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*).

Annex B

Definitions

Terms used in these Directions bear the same meaning as set out in the HTA's Codes of Practice, the parent Directive, the First Commission Directive and the Second Commission Directive, unless otherwise stated.

Autologous graft:	Means tissue or cells removed from and applied in the same person within the same surgical procedure.
Blood:	Means whole human blood collected from a donor and processed either for transfusion or for further manufacturing.
Blood component:	Means a therapeutic constituent of human blood (red cells, white cells, platelets and plasma) that can be prepared by various methods, but does not include lymphocytes intended for use for the purpose of haematopoietic stem cell transplantation.
Cells:	Means individual human cells or a collection of human cells when not bound by any form of connective tissue, including cell lines grown outside the human body but not including: – a. Gametes; b. Embryos outside the human body; or c. Blood and blood components.
Distribution:	Means transportation and delivery of tissues or cells intended for human applications. A person who, from any premises, controls the provision of services for transporting tissue or cells is to be taken to distribute tissue or cells on those premises.
Donation:	means donating human tissues or cells intended for human applications.
Donor:	means every human source, whether living or deceased, of human cells or tissues.

Export:	Means export from the United Kingdom to a place outside the United Kingdom.
Human Application:	In relation to tissue or cells, means use on or in a human recipient, including use in extracorporeal applications but not including use for autologous graft.
Import:	Means import into the United Kingdom from a place outside the United Kingdom.
Procurement:	means a process by which tissue or cells are made available.
Preservation:	means 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.
Processing:	means all operations involved in the preparation, manipulation, preservation and packaging of tissues or cells intended for human applications.
Serious adverse event:	<p>means any untoward occurrence which may be associated with the procurement, testing, processing, storage or distribution of tissue or cells intended for human application and which, in relation to a donor of tissue or cells intended for human application or a recipient of tissue or cells: –</p> <ul style="list-style-type: none"> (a) might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions, or (b) might result in, or prolong, hospitalisation or morbidity.
Serious adverse reaction:	means an unintended response, including a communicable disease, in a donor of tissue or cells intended for human application or a recipient of tissue or cells, which may be associated with the procurement or human application of tissue or cells and which is fatal, life-threatening, disabling,

incapacitating or which results in, or prolongs, hospitalisation or morbidity.

Source country:

Means the country from which the tissues and/or cells have been imported into the UK for human application.

Storage:

Means maintaining tissue or cells, whether by preservation or in any other way, for more than 48 hours.

Tissue or tissues:

Means all constituent parts of the human body formed by cells, but does not include:
–

- a. Gametes;
- b. Embryos outside the human body; or
- c. Organs or parts of organs if it is their function to be used for the same purpose as the entire organ in the human body.