



Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment

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Version 2

Preamble

This guide explains the requirements for licences and/or third party agreements which carry out the procurement, testing, processing, distribution, or export of tissues and cells for human application and for licences which store or import tissues and cells for human application.

The guide is based on the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended), and on the standards required under the Commission Directives 2004/23/EC, 2006/17/EC (amended by 2012/39/EU), 2006/86/EC (amended by (EU) 2015/565) and (EU) 2015/566.

Consent requirements are set out in accordance with the above legislation but also taking into account the requirements of the Human Tissue Act 2004 and the HTA code of practice. Establishments based in Scotland should refer to the authorisation requirements of the Human Tissue (Scotland) Act 2006.

Revision History

Version Number	Issue date	Summary of changes
V 1	12 November 2010	
V 1.1	June 2015	<p>Definition of an organ in the glossary revised in line with Directive 2010/53/EU.</p> <p>Standard condition number updated in paragraph 125.</p> <p>Update of Annex B to account for the amendment to donor testing requirements for HTLV (via Commission Directive 2012/39/EU)</p> <p>Removal of Annexes C&D which are no longer current.</p>
V 1.2	June 2017	<p>Minor amendments to paragraphs 72, 132 and 206 to reflect the HTA's revised codes of practice.</p>
V2	April 2018	<p>Version 2 introduces changes brought about by the Human Tissue (Quality and Safety for Human Application) (Amendment) Regulations 2018. These transpose Directives (EU) 2015/565 and (EU) 2015/566 which amend and introduce requirements relating to traceability and ensuring equivalent standards of quality and safety for imported tissues and cells.</p>

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Glossary / Definitions

Terms used in this document have the same meaning as set out in the HTA's codes of practice and the Directives, unless otherwise stated. Definitions marked with * are as defined within the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended).

Allogeneic use: Cells or tissues removed from one person and applied to another.

Autologous graft: The term is used throughout this guide in the way it is used by practitioners, i.e. meaning the removal and transplantation of tissues and cells from an individual and re-implantation into the same individual at a later date.

Autologous use: Cells or tissues removed from and applied to the same person.

Authorised personnel: Persons authorised to carry out specific tasks under a licence; this includes third parties working under a third party agreement. This authorisation is ultimately the responsibility of the DI, but in practice SOPs often may outline the type of staff eligible for carrying out specific tasks. Staff authorised to carry out a specific duty must have adequate knowledge and training.

Blood: Whole human blood collected from a donor and processed either for transfusion or for further manufacturing.

Blood component: 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 after haematopoietic stem cell transplantation.

Cells: 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: gametes; blood and blood components.

Critical: Potentially having an effect on the quality and/or safety of or having contact with the cells and tissues.

DI: Designated Individual, the individual designated on the HTA licence as the person under whose supervision the licensed activity is authorised to be carried on.

Direct use: Any procedure where cells are donated and used without any banking.

* **Distribution:** Transportation or delivery of tissues or cells to any person in or outside of the United Kingdom for human application. A person who, from any premises, controls the provision of services for transporting or delivering tissue or cells to any person in or outside of the United Kingdom for human application is to be taken to distribute tissue or cells on those premises.

Donation: Donating human tissues or cells intended for human application.

Donation identification sequence, SEC-DI: The first part of the Single European Code consisting of the EU tissue establishment code and the unique donation number.

Donor: Every human source, whether living or deceased, of human cells or tissues.

* **Emergency:** Any unforeseen situation in which there is no practical alternative other than to urgently import into the United Kingdom tissues and cells from a third country or to export from the United Kingdom to a third country tissues or cells for immediate application to a known recipient whose health would otherwise be seriously endangered.

* **End User:** A health care establishment or a unit of a hospital or another body which carries out human application of tissues and cells. End users are subject to licensing if they store tissue for longer than 48 hours.

EU Coding Platform: The IT platform hosted by the EU Commission which contains the EU Tissue Establishment Compendium and the EU Tissue and Cell Product Compendium.

EUTC: The product coding system for tissues and cells developed by the Union consisting of a register of all types of tissues and cells circulating in the Union and their corresponding product codes.

EU Tissue and Cell Product Compendium: The register of all types of tissues and cells circulating in the Union and the respective product codes under the three permitted coding systems (EUTC, ISBT128 and Eurocode).

EU tissue establishment code: The unique identifier for accredited, designated, authorised, or licensed tissue establishments in the Union. The tissue establishment code consists of an ISO country code and the tissue establishment number set out in the EU Tissue Establishment Compendium, as further specified in Annex VII to Directive 2015/565.

EU Tissue Establishment Compendium: The register of all tissue establishments which are authorised, licensed, designated or accredited by the Member States' competent authority or authorities and which contains the information about these tissue establishments as set out in Annex VIII to Directive 2015/565.

Expiry date: The date by which the tissues and cells can be applied, written in the format YYYYMMDD.

Facilities: These include clinical facilities, laboratory facilities, storage facilities, facilities for donation, facilities for reception and procurement, facilities for distribution, import and/or export, and facilities for staff.

Human Application: In relation to tissue or cells, means use on or in a human recipient, including

use in extracorporeal applications. It excludes the use of an autologous graft within the same surgical procedure.

HT Act: The Human Tissue Act 2004.

Importing tissue establishment, ITE: A tissue bank or a unit of a hospital or another body established within the Union which is a party to a contractual agreement with a third country supplier for the import into the Union of tissues and cells coming from a third country intended for human application.

LH: Licence Holder, means a person or corporate body who holds a licence under Schedule 1 of the Regulations.

* **One-off import:** The import of any specific type of tissue or cell which is for the personal use of an intended recipient or recipients known to the importing tissue establishment and the third country supplier before the importation occurs. Such an import of any specific type of tissue or cell shall normally not occur more than once for any given recipient. Imports from the same third country supplier taking place on a regular or repeated basis shall not be considered to be 'one-off imports'

Organ: A differentiated part of the human body, formed by different tissues, that maintains its structure, vascularisation and capacity to develop physiological functions with a significant level of autonomy. A part of an organ is also considered to be an organ if its function is to be used for the same purpose as the entire organ in the human body, maintaining the requirements of structure and vascularisation.

Organisation responsible for human application, ORHA: refer to end user above.

Pooling: The physical contact or mixing in a single container, of tissues or cells from more than one procurement from the same donor, or from two or more donors.

Premises: Location where licensable activities are carried out.

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

Procurement: A process by which tissue or cells are made available.

Procurement organisations: A health care establishment or a unit of a hospital or another body that undertakes the procurement of human tissues and cells and that may not be accredited, designated, authorised or licensed as a tissue establishment.

Product code: The identifier for the specific type of tissue and cell in question. The product code consists of the product coding system identifier indicating the coding system used by the tissue establishment (“E” for the EUTC, “A” for ISBT128, “B” for Eurocode) and the tissues and cells product number foreseen in the respective coding system for the product type, as further defined in Annex VII to Directive 2015/565.

Product identification sequence, SEC-PI: The second part of the Single European Code consisting of the product code, the split number and the expiry date.

Quality Manager: A person who is designated to coordinate and oversee the activities under the quality management system. He/she may monitor and advise on the performance of the quality management system and produces reports on performance, measuring against set indicators. The quality manager may also advise on changes and their implementation and provides training, tools and techniques to enable others to achieve quality.

Quality management: The coordinated activities to direct and control an organisation with regard to quality.

Quality management system: A set of processes that define the establishment’s approach to the management of the organisation. It should ensure continuous and systematic improvement through use of a quality system and quality review ‘tools’ such as audit and risk assessment, so that the establishment provides products and services which meet required standards.

Quality System: The organisational structure, defined responsibilities, procedures, processes, and resources for implementing quality management and includes all activities which contribute to quality, directly or indirectly.

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

Raw data: Original data in unmodified form, such as temperature monitoring read-outs, environmental monitoring records etc. These must be retained for a minimum of ten years in their original format. After this period, raw data may be stored in consolidated format for traceability purposes.

Regulations: Used throughout to refer to the Human Tissue (Quality and Safety for Human Application) Regulations 2007 as amended by The Human Tissue (Quality and Safety for Human Application) (Amendment) Regulations 2018.

Released for circulation: Distribution for human application or transfer to another operator, e.g. for further processing with or without return.

Serious adverse event, SAE: 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:

- 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, SAR: 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.

Single European Code, SEC: The unique identifier applied to tissues and cells distributed in the Union. The Single European Code consists of a donation identification sequence and a product identification sequence, as further specified in Annex VII to Directive 2015/565.

SLA: Service level agreement. This term is frequently used in this guide for agreements between two licensed entities.

SOP, standard operating procedure: Written instructions describing the steps in a specific process, including the materials and methods to be used and the expected end product.

Split number: The number which distinguishes and uniquely identifies tissues and cells having the same unique donation number and the same product code and originating from the same tissue establishment, as further defined in Annex VII to Directive 2015/565.

* **Storage:** Maintaining tissue or cells, whether by preservation or in any other way, for more than 48 hours under appropriate controlled conditions until distribution.

Third Country: a country which is not an EEA state or Gibraltar.

* **Third country supplier, 3CS:** A person in a third country who has an agreement with an importing licence holder for exporting tissues or cells intended for import into the United Kingdom for human application.

Third Party: A person or corporate body with whom a LH, or the DI on behalf of the LH, has a third party agreement. A third party is defined here as an entity which is not licensed for human application by the HTA.

Third Party Agreement, TPA: An agreement in writing between a LH, or the DI on behalf of the LH, and another person or corporate body who do not hold an HTA licence for human application. A TPA is entered into for the purpose of securing adherence to the specified requirements of the Regulations and Directives, and under which the other person:

- a) carries on a licensed activity (other than storage or import), on behalf of the LH i.e. procures, processes, tests, distributes, or exports tissues and/or cells on behalf of the LH; or
- b) supplies to the LH any goods or services which may affect the quality or safety of tissue or cells.

Third Party Premises: Any premises (other than premises to which the licence relates):

- a) on which a third party procures, tests, processes or distributes, or from which a third party exports from the United Kingdom to a third country, tissue or cells on behalf of any person authorised by a licence to carry on that activity; or
- b) from which a third party provides any goods or services which may affect the quality or safety of tissue or cells to any person in connection with licensed activities carried on by that person.

Tissue or Tissues: All constituent parts of the human body formed by cells, but does not include:

- a) gametes; or
- 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.

Tissue establishment, TE: A tissue bank or a unit of a hospital or another body where activities of processing, preservation, storage, distribution or import/export are undertaken. It may also be responsible for procurement or testing of tissues and cells.

Traceability: The ability to locate and identify the tissue/cell during any step from procurement, through processing, testing and storage, to distribution to the recipient or disposal, which also implies the ability to identify the donor and the tissue establishment or the manufacturing facility receiving, processing or storing the tissue/cells, and the ability to identify the recipient(s) at the medical facility/facilities applying the tissue/cells to the recipient(s). Traceability also covers the ability to locate and identify all relevant data relating to products and materials coming into contact with those tissues/cells.

Unique donation number: The unique number attributed to a specific donation of tissues and cells in line with the system in place in each Member State for allocating such numbers, as further specified in Annex VII to Directive 2015/565.

Validation (or 'qualification' in the case of equipment or environments): Establishing documented evidence that provides a high degree of assurance that a specific process, SOP, piece of equipment or environment will consistently produce a product meeting its predetermined specifications and quality attributes; a process is validated to evaluate the performance of a system with regard to its effectiveness based on intended use.

Within the same centre: All steps from procurement to human application are carried out under the same responsible person, quality management system and traceability system, within a healthcare

centre comprising at least an accredited, designated, authorised, or licensed tissue establishment and an organisation responsible for human application at the same location.

General requirements for licensed establishments

The role of the Designated Individual

1. A Designated Individual (DI) must be appointed having qualifications and responsibilities as provided in the Human Tissue (Quality and Safety for Human Application) Regulations 2007 ([the Regulations](#)).
2. The DI has a statutory duty to secure that:
 - a) the other persons to whom the licence applies are suitable persons to participate in the carrying-on of the licensed activities;
 - b) suitable practices are used in the course of carrying out the licensed activities;
 - c) the conditions of the licence are complied with;
 - d) ensuring that licensable activities carried out by third parties are subject to suitable practices and are carried out by suitable persons; and
 - e) the requirements of [Regulation 13\(1\)](#) relating to information and confidentiality are complied with.
3. In addition, the DI has responsibility for:
 - a) ensuring that tissues and cells for human application in the establishment are procured, tested, processed, stored, distributed and imported/exported in accordance with these requirements set out here;
 - b) ensuring that the establishment carries out all appropriate control measures as required by the HTA to ensure adherence to [the Regulations](#);
 - c) keeping a record of the establishment's activities (as outlined in the [register and reporting obligations section](#)) and submitting to the HTA an annual report on these activities;
 - d) notifying the HTA of any serious adverse event or serious adverse reaction within 24 hours of discovery (see section on [serious adverse events and reactions](#));
 - e) ensuring that the establishment puts in place and updates a quality management system in accordance as outlined in the [quality management section](#);
 - f) ensuring that the donor selection and evaluation is carried out in accordance with [the Regulations](#);
 - g) ensuring that the acceptance or rejection of tissues and cells for human application is carried out in accordance with [the Regulations](#);
 - h) ensuring (in conjunction with the LH) that third party agreements are in place and maintained whenever a third party undertakes one of the licensable activities on behalf of

- the licensed establishment, or supplies any goods or services which affect the quality or safety of tissues and cells (see section on [third party agreements](#));
- i) ensuring that any third party with whom there is a third party agreement is made aware of, and provided with, copies of all relevant HTA Directions, regulatory alerts or other communications from the HTA without delay;
 - j) supervising the establishment's system for verification that tissues and cells meet all appropriate specifications prior to release (see [storage and release](#) of products section);
 - k) approving the documented risk assessment undertaken to determine the fate of all stored tissues and cells following the introduction of any new donor selection or testing criterion or any significantly modified processing step (see [storage and release of products](#) section); and
 - l) ensuring, in conjunction with the LH, that all imports of human tissues and cells from non-EEA states meet standards of quality and safety equivalent to those set down in [the Regulations](#).
4. 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 LH must immediately apply to the HTA for a licence variation to nominate a substitute DI. This nominated substitute DI must not commence their post unless and until the HTA decides that they are suitable.

The role of the Licence Holder

5. The LH has responsibility for:
- a) entering into and maintaining third party agreements on behalf of the establishment in line with the requirements set out in the section on [third party agreements](#). This responsibility can be delegated to the DI, but the LH will nonetheless retain responsibility for ensuring that third party agreements comply with requirements ensuring that any information from which a donor or recipient may be identified is kept confidential and not disclosed other than in circumstances permitted by law (see section on [data protection and confidentiality](#));
 - b) making any necessary application to the HTA for approval for direct distribution and/or import/export from where procurement takes place to an organisation responsible for human application (see section on [distribution and recall](#));
 - c) ensuring that the establishment complies with the requirements relating to serious adverse events and reactions (see section on [serious adverse events and reactions](#));
 - d) ensuring that procurement organisations and end users have the necessary procedures to retain records of tissues and cells and to comply with the notification requirements for serious adverse events and reactions;
 - e) ensuring, in conjunction with the DI, that all imports of human tissue and cells from non-EEA states meet the standards of quality and safety equivalent to those required for tissues and cells procured, tested, processed, stored and distributed within the EEA.

6. Further, it is the responsibility of the LH to support the DI, to ensure that human tissues and cells, intended for human application, are procured, tested, processed, stored, distributed and imported or exported in accordance with [the Regulations](#).
7. If the licence holder is a corporate body, the HTA requires that a person is nominated to act as a point of contact for the corporate licence. The HTA terms this person the corporate licence holder contact and they should be in a position to act as a representative of the corporate body.

Organisational and operational requirements

8. A tissue establishment must have an organisational structure and operational procedures appropriate for the activities for which the licence has been granted; there must be an organisational chart which defines accountability and reporting relationships.
9. A documented quality management system must be in place in respect of all activities for which a licence was granted.
10. Risk inherent in the use and handling of biological material must be identified and minimised, so that adequate quality and safety for the intended purpose of the tissues and cells can be ensured.
11. Every tissue establishment must have access to a nominated registered medical practitioner to advise on and oversee the establishment's medical activities such as donor selection, review of clinical outcomes for donor or recipients and interaction with clinical users.
12. Where licensable activities are undertaken by unlicensed establishments on behalf of licensed ones, this must take place under [third party agreements](#). The licensed establishment and the DI must put in place suitable control measures for the activities carried out.
13. Where goods or services that influence critical quality or safety parameters of the tissues and cells are supplied to a licensed establishment by a third party, suitable [third party agreements](#) and control measures should be put in place by the DI and LH.
14. There must be a documented [release system](#) in place which is supervised by the DI, and which ensures that tissues and cells meet appropriate quality and safety criteria before their distribution to end users.
15. There must be a documented system in place that ensures that every unit of tissue or cells can be identified at all stages from procurement through to end use.
16. In the event of [termination of activities](#), agreements and procedures must be put in place which ensure that full traceability data are maintained for a period of 30 years following end use or disposal.

Data Protection and confidentiality

17. Information must be kept up to date and corrected immediately once any discrepancy is identified. It must be kept secure so that there is no possibility of unauthorised additions, deletions, changes or transfer. It must be available for tracing donations.
18. Information that could allow identification of a donor or recipient can only be disclosed in the following circumstances:
 - a) where the information is kept anonymous, or made subject to a court order, or otherwise required by law;
 - b) to the HTA or a person acting on the HTA's authority;
 - c) to a tissue establishment in order to trace a donation, to a licence holder for the purposes of fulfilling the licence, or to a third party for the purposes of fulfilling the third party agreement;
 - d) to the donor or recipient where consent has been given;
 - e) where it is necessary for any proceedings, reporting a suspected offence, co-operating with a police investigation, or for investigating a serious adverse event or serious adverse reaction;
 - f) if made by a LH or DI under HTA directions;
 - g) when information has been lawfully made available to the public before disclosure is made.
19. Disclosure of information outside these circumstances is a criminal offence unless the person can prove that he took all reasonable precautions and exercised all due diligence to avoid the offence.

Register and reporting obligations

20. Licensed establishments must keep a record of their activities, including:
 - a) the types and quantities of tissues and/or cells procured, tested, processed, stored, distributed, imported or exported or otherwise disposed of;
 - b) the origin and destination of the tissues and cells intended for human applications;
 - c) a record of whether the tissues and cells are for autologous or allogeneic use;
 - d) the coded data assigned to each donor and donation of tissues and cells.
21. Establishments must ensure that third parties carrying out licensable activities on their behalf also maintain the above records and report to the licensed establishment and/or the HTA upon request (see section on [third party agreements](#)).
22. Records should be stored in a format which ensures that the information retained can be easily extracted and submitted electronically to the HTA as an annual report covering the activity of the

calendar year, submitted by the 31 January of the following year. This report must be in the format specified by the HTA.

EU TE Compendium and changes to activities carried out under a human application licence

23. All establishments that hold a human application licence are listed in the [EU Tissue Establishment \(TE\) compendium](#). This includes a record of the activities that an establishment is licensed to undertake and each of the tissue types that an establishment is authorised to undertake these activities for.
24. It is the HTA's responsibility to keep the TE compendium up to date and to make any updates required. Establishments should check that their information, as listed in the TE compendium is accurate and notify the HTA if any of the information appears to be incorrect.
25. All establishments are required to notify the HTA of intended changes to licensable activities and must not undertake these changes until authorised in writing by the HTA to do so..
26. Standard condition 14 of any HTA human application licence requires that whenever a new type of tissues or cells is to be procured, tested, processed, stored, distributed, imported or exported by the establishment, the DI must first notify the HTA. The new type of tissues and/or cells may not be procured, tested, processed, stored, distributed, imported or exported by the establishment until the HTA is satisfied that the establishment has suitable premises and employs suitable practices to carry out the proposed activity in respect of these tissues or cells.
27. Once the changes referred to in paragraph 26 have been authorised, the HTA will update the TE compendium within 10 working days.

Quality management

28. Licensed establishments must have a quality management system (QMS) which ensures that tissues and cells are fit for their intended use, and do not place patients or donors at risk. Processes carried out must not render the cells clinically ineffective or harmful.
29. The extent of the QMS should be proportionate to the nature of the operations carried out, for example cell preparation processes will normally require more control elements and a more extensive QMS than most storage activities.
30. The critical quality attributes of the given tissues or cells must be defined and described, as well as the methodologies required to achieve those specifications. Based on these requirements an establishment should identify and document all critical activities.
31. Reagents and material required to achieve or maintain critical quality attributes of tissues and cells must be listed and subject to acceptance controls. All critical equipment should be identified and be subject to controls described in the equipment section.
32. For every critical activity, the materials, equipment and personnel involved must be identified and documented.
33. The DI is responsible for the implementation of the QMS, but the participation and commitment of all staff working under the licence are essential for an effective system.
34. The quality system should include the following documentation:
 - a) a quality manual which provides an overview of the quality system;
 - b) standard operating procedures;
 - c) guidelines, e.g. from relevant professional bodies or advisory committees;
 - d) training and reference manuals;
 - e) reporting forms;
 - f) donor records and any records required by the HTA;
 - g) information on the final destination of tissues and cells;
 - h) a risk management system;
 - i) non-conformances and incident monitoring and follow-up, including serious adverse event and reaction management;
 - j) a mechanism to control changes to ensure these do not adversely affect the quality and safety of the tissues and cells and which allows for the mitigation of risk associated with change.
30. The establishment should consider the appointment of a quality manager to coordinate the activities required to meet quality standards. Ideally the quality manager should not be directly involved in the activities of the tissue establishment in order to foster an independent approach, e.g. to audits. The person appointed as quality manager may be an existing member of staff with other duties, but with sufficient ring-fenced time to carry out the duties of quality manager.

Quality review

35. An audit system must be in place for the licensed activities. Adherence to the standard operating procedures and the regulatory requirements must be audited by trained and competent persons in an independent way, at least every two years. A rolling schedule of audits based on a two year cycle would achieve this. The DI should put systems in place that ensure audits maintain impartiality, an example would be staff auditing tasks that they do not carry out themselves. Findings and corrective actions must be documented.
36. Deviations from the critical quality attributes must lead to documented investigations, which include a decision on possible corrective and preventative actions. The fate of non-conforming tissues and cells must be decided in accordance with written procedures supervised by the DI and recorded. All affected tissues and cells must be identified and accounted for.
37. Corrective and preventative actions must be documented, initiated and completed in a timely and effective manner and they should be assessed for effectiveness after implementation.
38. The tissue establishment should have processes in place to review the performance of the quality management system to ensure continuous and systematic improvement. This review should include, but not be limited to, consideration of the results of any investigations into suspected serious adverse events or reactions. The results of the quality review must be recorded and maintained, including all decisions and proposed actions related to the improvement of the quality management system.
39. The establishment must complete a self-assessment form assessing the establishment against the HTA's compliance standards at least every 12 months. All self-assessment forms must be retained, and provided to the HTA on request for example prior to an inspection.

Personnel

40. There must be sufficient suitably qualified personnel to carry out all the tasks. All personnel should have clear, documented and up-to-date job descriptions. The establishment must maintain personnel records that comprise all relevant employment information, training records and registration with any professional or statutory bodies.
41. Personnel should receive initial and continued training appropriate to the duties assigned to them. Training programmes should be in place. The effectiveness of all training programmes should be monitored by regular assessments of personnel competency. Training should be documented and training records maintained. Personnel should also be trained in quality principles and legal and ethical aspects relevant to their work.
42. Personnel should have relevant knowledge of microbiology and hygiene and should be constantly aware that microbial contamination of themselves, donors, recipients, tissues, cells

and premises should be avoided. Hygiene instructions must be present in each department and these instructions should be understood and followed by all individuals.

Equipment and materials

43. The establishment must ensure that it has the equipment and materials necessary to effectively carry out the activities for which it is licensed.
44. Medical devices, equipment and materials must meet the requirements of Council [Directive 93/42/EEC](#) of 14 June 1993 and [Directive 98/79/EC](#) of the European Parliament and of the Council of 27 October 1998 for in vitro diagnostic medical devices.
45. All equipment that might influence the critical quality and safety parameters of tissues and cells must be designed, validated and maintained to suit its intended purpose and to minimise any hazard to donors, recipients or operators. It should permit effective cleaning. Maintenance, monitoring, cleaning and calibration should be regularly undertaken. A traceable standard should be used for calibration, if available.
46. All critical equipment must have set operational limits (such as temperature, humidity etc.) and must be monitored.
47. Procedures for the operation of each piece of critical equipment must be available. These should detail the action to be taken in event of malfunctions or failure.
48. Specifications of critical reagents and materials must be documented, and suppliers must be chosen based on their ability to meet those specifications. The establishment should have a list of accepted suppliers of critical reagents and materials. Suppliers should provide a certificate of compliance for every lot of materials.
49. Inventory records must be kept for traceability and to prevent use of materials after their expiry date.
50. Apparent deviations in the quality and performance of equipment and materials should be investigated and documented. The outcomes of these investigations should be reported in a timely manner to the DI and corrective actions taken. For relevant deviations a notice should be sent to the manufacturer and, where appropriate, the [HTA should be informed](#).
51. All relevant data relating to products and material coming into contact with tissues and cells must be recorded and traceable in accordance with the requirements set out in the [traceability section](#).
52. When reusable instruments are used, a validated cleaning and sterilisation procedure for removal of infectious agents must be in place.

53. Wherever possible, CE marked medical devices must be used and staff must have received training on the use of such devices. Where CE marked devices are not available or suitable for the purpose, appropriate validation must be undertaken.

Facilities and premises

54. Facilities must be fit for purpose and conform to health and safety requirements. They must be risk assessed. Consideration should be given to the need for contingency, where critical activities are concerned.
55. The tissue establishment must have written policies and procedures for the maintenance of its premises and facilities which include:
- a) controlled access;
 - b) cleaning and maintenance;
 - c) waste disposal;
 - d) re-provision of services and action to be taken in event of an emergency;
 - e) health, safety and welfare of all staff;
 - f) regular review and risk assessment of facilities.
56. Where tissues or cells, or any medium coming into direct contact with them, are exposed to the environment during processing, without a subsequent microbial inactivation process, then this must be in a working environment with air particle counts and microbial colony counts equivalent to those of Grade A as defined in the current [European Guide to Good Manufacturing Practice \(GMP\), Annex 1](#) of Directive 2003/94/EC. The background environment for the processing of the tissue must be at least equivalent to Grade D. To demonstrate compliance with the requisite air particle requirements measurements must be taken at rest and in operation.
57. Clean rooms and clean air devices should be routinely monitored in operation. For Grade A zones particle monitoring should be undertaken for the full duration of critical processing. Where this cannot be technically achieved due to the nature of the operations, reasons must be documented and simulated operations or media fills must be carried out.
58. A validated cleaning protocol for processing environments must be in place and processing activities must be organised so as to ensure that risk of cross-contamination between different donations and batches is minimised.
59. A less stringent environment than specified in paragraph 56 may be acceptable where:

- a) a validated microbial inactivation or validated terminal sterilisation process is applied; or
 - b) where it is demonstrated that exposure in a Grade A environment has a detrimental effect on the required properties of the tissue or cell concerned; or
 - c) where it is demonstrated that the mode and route of application of the tissue or cell to the recipient implies a significantly lower risk of transmitting bacterial or fungal infection to the recipient than with cell and tissue transplantation; or
 - d) where it is not technically possible to carry out the required process in a Grade A environment (for example, due to requirements for specific equipment in the processing area that is not fully compatible with Grade A).
60. In each case, an environment must be specified. It must be demonstrated that the chosen environment is suitable for maintaining critical quality and safety attributes, taking into account the intended purpose, mode of application and immune status of the recipient.
61. Garments and equipment for personal protection and hygiene must be provided in each relevant department of the tissue establishment along with written hygiene and gowning instructions. For processing environments, garments should support the designated air quality grades, in terms of cover provided, shedding and sterility.
62. Where tissues and cells are stored, the conditions necessary to maintain the required tissue and cell properties must be defined, and tolerance limits set.
63. Storage areas should be designed to avoid or minimise contact with chemical or atmospheric contamination and any known potential sources of infection.
64. There must be emergency and backup procedures to deal with any failure of equipment required to maintain storage conditions.
65. Storage facilities must separate and distinguish tissues and cells that are held in quarantine from those that are released and those that are rejected. Where necessary there must be separate storage provisions for tissues and cells collected in accordance with special criteria, such as positive donor serology.
66. Control measures must extend to packaging areas, to ensure no damage, contamination or mix-up of tissues or cells occurs.

Documentation and records

67. Documentation and records provide evidence that all aspects of the QMS have been implemented satisfactorily and that tissues and cells conform to the critical quality attributes that have been defined.

68. Records must ensure that all steps are traceable, including coding, donor eligibility, procurement, testing, processing, preservation, storage, transport, distribution or disposal, import and export.
69. The document control and records system must result in clearly defined and effective documentation, which includes correct records and registers.
70. All quality documents must be subject to document control, with date, author, approver and version history evident. Quality documents (SOPs, risk assessments etc.) must be regularly reviewed; this should occur at least every two years. The document control system must further ensure that only current versions of documents are in use.
71. All changes to documents and records must be reviewed, dated, approved, documented and implemented by suitable personnel.
72. The management of records must be described in an SOP. The SOP must ensure that patient records and records of all critical quality parameters and procedures are kept for the required time. The SOP must describe identification, collection, indexing, access, storage, maintenance, confidentiality and safe destruction of records. Audits and database validations should be undertaken to ensure records are accurate.
73. Records must be legible and indelible and may be handwritten or transferred to another validated system, such as a computer or microfilm.
74. All records, including raw data, such as original temperature monitoring records, which are critical to the safety and quality of the tissues and cells, must be kept for at least 10 years after any expiry date, clinical use or disposal of the tissues and cells.
75. Specific record requirements for traceability are set out in [paragraph 207](#).

Consent

76. The establishment must comply with the [Human Tissue Act 2004](#) (the HT Act) and the HTA's codes of practice, particularly the code of practice on consent ([Code A](#)) and the code of practice on donation of allogeneic bone marrow and peripheral blood stem cells for transplantation ([Code G](#)).
77. The establishment must ensure that consent information is given to a prospective donor prior to the donation (or an individual or individuals giving consent on behalf of a donor) and in a way that is compliant with the HT Act, the HTA Consent code and, where applicable, the HTA BM donation code.
78. The establishment must 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 must cover at least the purpose and nature of the donation, its consequence and risks, any analytical tests that 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;
 - d) the prospective donor must be informed of the necessity for obtaining his or her prior consent to the procurement.
79. 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.
80. 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:
 - a) understood the information provided;
 - b) had an opportunity to ask questions and been provided with satisfactory responses.
81. Tissues and cells must not be procured until it has been verified that consent has been lawfully obtained. Where consent is obtained by personnel at an unlicensed establishment, the licensed establishment must satisfy itself, whether directly or indirectly through SLAs and/or SOPs that the consent provisions have been fulfilled.

Donor selection, evaluation and testing

Selection criteria for donors of tissues and cells

82. Selection criteria for donors must be based on an analysis of risks related to the application of the specific tissues or cells. Indicators of these risks must be identified by biological testing, review of the medical and behavioural history, physical examination, post-mortem examination (for deceased donors) and any other appropriate investigation.
83. Donors must be excluded from donation if any of the criteria in [Annex A](#) apply, unless donation is justified on the basis of a documented risk assessment approved by the DI.
84. There must be documented procedures for donor selection which set out the selection and exclusion criteria, the reviews and investigations to be carried out and who is responsible for donor selection.
85. A corresponding record must be created for each donor evaluation procedure carried out in accordance with paragraph [94](#).
86. If donor selection is carried out by staff or clinicians not employed by the licensed establishment, there must be written agreements which specify a donor evaluation procedure in accordance with paragraph [82](#).
87. The establishment must 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 HT Act which allows the LH in certain circumstances to receive payment for the transportation, removal, preparation, preservation or storage of certain tissues and cells for transplantation provided that the terms of the LH's licence does not expressly prohibit such payment.

Allogeneic donor evaluation

88. A person authorised by the DI must collect and record the donor's relevant medical and behavioural information according to the requirements set out in the paragraphs 85 to 87.
89. In order to acquire the appropriate information, different relevant sources must be used, including at least an interview with the donor, and a review of the following when appropriate:

- a) the clinical records of the donor;
- b) an interview with a person who knew the donor well, for deceased donors;
- c) an interview with the treating physician;
- d) an interview with the general practitioner;
- e) the autopsy report.

Interviews must be performed by a registered healthcare professional.

- 90. 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 be sufficient in themselves to exclude the donor. These must be assessed in the light of the donor's medical and behavioural history.
- 91. The complete donor records must be reviewed and assessed for suitability and signed by a registered healthcare professional.

Donor documentation

- 92. For each donor, there must be a record containing:
 - a) the donor identification (first name, family name and date of birth – if a mother and child are involved in the donation, both the name and date of birth of the mother, and the name, if known, and date of birth of the child);
 - b) age, sex, medical and behavioural history (the information must be sufficient to allow application of the exclusion criteria, where required);
 - c) outcome of body examination, where applicable;
 - d) haemodilution formula, where applicable;
 - e) evidence of consent, including the purpose for which the tissues and cells may be used, and any specific instructions for use/disposal;
 - f) clinical data, laboratory test results and the results of other tests carried out;
 - g) if a post mortem examination was performed, the results must be included in the record (for tissues and cells that cannot be stored for extended periods, a preliminary verbal report of the autopsy must be recorded);
 - h) for haematopoietic progenitor cell donors, the donor's suitability for the chosen recipient must be documented. For unrelated donations, when the procurement organisation has limited access to recipient data, the transplanting organisation must be provided with donor data relevant for confirming suitability.
- 93. Donor records required for full traceability must be kept for a minimum of 30 years after clinical use or disposal, in an archive and format which ensures continued accessibility during that time.

Laboratory tests required for donors

94. Donors of tissues and cells must undergo the serological tests in accordance with the requirements of Annex II Directive 2006/17/EC, which is reproduced in [Annex B](#) of this document.
95. The biological tests must be carried out in accordance with the general requirements set out in [point 2 of Annex B](#). These represent minimal testing requirements only. Establishments are responsible for ensuring that any additional tests required by national guidelines or their organisational governance framework are carried out.
96. The HTA advises that the following test regimen for allogeneic tissues or cells represents fulfilment of the requirements of with Annex B:
 - a) tests must be carried out on a blood sample of the donor. All tests must at first instance be immunological as set out in point 1.1 of Annex B, even if point c. below is applied;
 - b) where samples can be stored for long periods, repeat testing on a donor blood sample taken after an 180 day interval must be carried out;
 - c) where the original sample is additionally tested by nucleic acid amplification technique (NAT) for HIV, Hepatitis B and Hepatitis C a repeat sample need not be taken. Under these circumstances the Syphilis immunological screen need only be carried out on the first donation sample;
 - d) donors of bone marrow and peripheral blood stem cells need only be screened on the donation sample even though material or preparations such as donor lymphocyte infusions may be stored for longer. The HTA nevertheless considers it best practice to carry out additional NAT testing wherever possible;
 - e) where cord blood is stored for long periods, repeat sampling and testing must be carried out on a new donor blood sample taken after an interval of 180 days or the donation sample must additionally be tested using NAT.
97. Where matched stored cord blood for allogeneic use is imported for the treatment of life threatening conditions and where repeat testing or NAT testing has not taken place, additional NAT tests must be carried out wherever there is access to blood from the original maternal donation sample or to a sample of the unprocessed cord blood.
98. Any 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.

Procurement

Procurement procedures for tissues and cells

99. Procurement of human tissues and cells must be carried out by registered healthcare professionals. They must have the necessary experience for undertaking the procurement procedure, either evidenced by their general job responsibilities or by having completed a documented training programme as agreed by the DI with the input of a clinical team specialising in the tissues and cells to be procured.
100. The licensed establishment must have written agreements with the staff or clinical teams responsible for tissue and cell procurement, unless they are employed by the same establishment, specifying:
- a) the types of tissues and cells and/or test samples to be procured;
 - b) the protocols to be followed.
101. There must be an SOP to ensure that, prior to the procurement of tissues and cells, an authorised person from the procuring establishment verifies and records:
- c) that consent for the procurement has been obtained in accordance with the HT Act and the HTA consent code;
 - d) how and by whom the donor has been reliably identified;
- and, where available at that time:
- e) that the assessment of the selection criteria for donors has been carried out as detailed in [Annex A](#);
 - f) that the assessment of the laboratory tests required for donors has been carried out as detailed in [Annex B](#).
102. There must also be SOPs describing the procedures for:
- a) procurement;
 - b) packaging;
 - c) labelling;
 - d) transportation of the tissues and cells;
 - e) transportation of tissue/cell samples to testing laboratories;
 - f) reporting of serious adverse events and/or reactions.
103. Procurement procedures must be suitable for the type of tissue/cell donated and must protect the properties of the tissues or cells required for their ultimate clinical use.

104. Procurement procedures must minimise the risk of microbiological or other contamination of tissues and cells, including the risk posed by the procurement facilities, particularly when tissues and cells cannot subsequently be sterilised. Policies and procedures must also be in place to minimise the risk of tissue or cell contamination by staff who might be infected with transmissible diseases.
105. Procurement premises must be risk assessed. Where procurement premises are not specified as part of an existing licence or third party agreement, i.e. where procurement takes place at many different locations which are not a priori identified, a documented risk assessment in respect of contamination and health and safety risks must be carried out by the procurer prior to each procurement episode. This risk assessment can be undertaken and documented with the help of a proforma authorised by the DI.
106. For deceased donation, the area of access must be restricted and a local sterile field using sterile drapes must be used. Staff conducting procurement must be clothed appropriately for the type of procurement. Usually, this will extend to being scrubbed, gowned in sterile clothing and wearing sterile gloves, face shields and protective masks.
107. 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 so as to ensure that the required biological and/or physical properties of the tissues or cells are retained.
108. Once the tissues and cells have been retrieved from a deceased donor, the body must be reconstructed so that it is as similar as possible to its original anatomical appearance. Where appropriate, additional staff and equipment necessary for body reconstruction of deceased donors must be made available.
109. In the case of living donors, procurement must take place in an environment that ensures their health, safety and privacy.
110. Any adverse event 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. The [reporting obligation to the HTA](#) must also be adhered to.
111. Only sterile instruments and devices must be used for tissue and cell procurement. Material and equipment must conform to the principles set out in the [equipment section](#).

Procurement records

112. The organisation performing the procurement must produce a procurement report, which is passed on to the tissue establishment. This report must contain at least:
- the identification, name and address of the tissue establishment to receive the tissue/cells;
 - donor identification data (including how and by whom the donor was identified);
 - description and identification of procured tissues and cells (including samples for testing);
 - identification of the person who is responsible for the procurement session, including signature;
 - date, time (where relevant, start and end) and location of procurement and procedure used, including any incidents that occurred;
 - environmental conditions at the procurement facility including the description of the physical area where procurement took place and, for ad hoc procurement, the documented risk assessment undertaken to determine suitability of the premises;
 - for deceased donors, conditions under which the cadaver is kept: refrigerated (or not), approximate time of start and end of refrigeration;
 - ID/batch numbers of reagents and transport solutions used;
 - for deceased donors, the date and time of death.
113. All the records must be treated in accordance with the principles set out under [documentation and records](#) and donor records must be kept as described in paragraphs [92 and 93](#).
114. A unique identifying code must be allocated to the donor and the donated tissues and cells, during procurement or at the tissue establishment. To ensure proper identification of the donor and the traceability of all donated material, a register of codes must be kept. Specific requirements relating to coding are set out in the section on [traceability and coding](#).
115. If tissue and cells are retrieved from a deceased donor by procurement teams operating for two or more tissue establishments, there needs to be an appropriate traceability system across procurements. This will require all tissue establishments to ensure robust traceability links between the donation identification numbers allocated by each tissue establishment procuring or receiving tissue and cells originating from the same deceased donor.

Transport following procurement

116. Organisations responsible for the transport and delivery of tissues or cells from procurement organisation to tissue establishment must adhere to the general transport requirements outlined in paragraphs [162 to 164](#).

117. The following outlines labelling requirements following procurement.

Labelling of the procured tissue or cells

118. At the time of procurement, every package containing tissues and cells must be labelled. The primary tissue or cell container must indicate:

- a) the donation identification or code; and
- b) the type of tissue or cells.

Where the size of the package permits, the following information must also be provided, otherwise it must be provided on a separate sheet accompanying the primary package:

- 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';
- e) in the case of directed donations, the label must identify the intended recipient.

Labelling of the shipping container

119. Every shipping container must be labelled at least with:

- a) a statement that the package contains tissue or cells and HANDLE WITH CARE;
- b) the identification of the establishment from which the package is being transported (address and phone number) and a contact person in event of problems;
- c) the identification of the destination establishment (address and phone number) and the person to be contacted to take delivery of the container;
- d) the date and time of the start of transportation;
- e) specifications concerning conditions of transport relevant to the quality and safety of the tissue or cells;
- f) in the case of all cellular products, the following indication: DO NOT IRRADIATE;
- g) when a product is known to be positive for a relevant infectious disease marker, the following indication: BIOLOGICAL HAZARD;
- h) in the case of autologous donors, the following indication: 'FOR AUTOLOGOUS USE ONLY';
- i) specifications concerning storage conditions (such as DO NOT FREEZE).

Reception at the tissue establishment

120. Tissue establishments must ensure that human tissues and cells are correctly identified at all times. Unless subject to one of the exemptions outlined in the section on the [European coding system](#), establishments must allocate a SEC-DI after procuring the tissues and cells, or when receiving them from a procurement organisation.
121. In all other cases, each delivery or batch of tissues or cells must be assigned an identifying code to ensure traceability.
122. Tissue establishments must have a receipt SOP for tissues and cells. Arrival at the tissue establishment must be documented, and the receipt procedure must ensure that the consignment is verified against the specifications of the receiving tissue establishment and the [labelling requirements](#) set out above.
123. The recipient should verify and record:
 - a) that correct tissue or cells have been received and adequate labelling information was provided;
 - b) time spent in transit, including any deviations from the maximum permissible transit time – transit time is the entire time spent in the shipping container including after receipt at the hospital;
 - c) intact packaging;
 - d) evidence that the required transit conditions were met (i.e. if the consignment was on ice, it should be recorded whether any ice remained in the shipping container);
 - e) conformance with other technical requirements or criteria considered by the tissue establishment to be critical for the maintenance of acceptable quality;
 - f) conformance of any test samples (including donor blood) with the transport and labelling requirements;
124. Where an establishment has received tissues and cells from another EU TE and there is a significant non-compliance relating to the SEC, this must be reported to the HTA.
125. Deviations should be recorded and followed up, any serious incidents, resulting for example in the loss of highly matched tissue or large quantities of unmatched tissue should be [reported to the HTA](#).
126. Tissues and cells must be quarantined until these, along with the associated documentation, have been verified as conforming to requirements.
127. For tissue establishments receiving tissues or cells not yet released for end use this must include review of donor testing results, behavioural information and procurement information

against the selection criteria. Acceptance of the donation needs to be carried out by persons authorised by the DI or LH.

128. The data that must be registered at the tissue establishment include:
- a) the [donor documentation](#): including consent/authorisation (including consent for other scheduled purposes under the HT Act such as research and any disposal requirements where applicable);
 - b) the [procurement record](#);
 - c) for allogeneic donors, the documented outcome of the review of the donor evaluation against the selection criteria.
129. The tissue establishment must have documented procedures for the management and segregation of non-conforming consignments, or those with incomplete test results, to ensure that there is no risk of contamination of other tissues and cells being processed, preserved or stored.
130. Establishments should carry out a documented risk assessment to determine the fate of tissues and cells that do not comply with required specifications. This should include any rationale for continuing to process or store non-conforming tissues and cells.

Tissue and cell preparation processes

Authorisation of tissue and cell preparation processes

131. Establishments must provide the HTA with evidence that any new cell or tissue preparation process is subject to the quality control measures outlined in paragraphs [30 to 32](#) and is validated in accordance with the principles set out in paragraphs [133 and 134](#) below.

Processing

132. The processing activity must take place on the context of a suitable quality management system, and critical parameters need to be identified and described as set out in paragraphs [30 to 32](#).
133. The critical processing steps must be identified and validated and must not render the tissues or cells clinically ineffective or harmful to the recipient. Validation may be based on studies performed by the establishment itself, or on data from published studies or, for well established processing methods, by retrospective evaluation of the clinical results for tissues supplied by the establishment.
134. It has to be demonstrated that the validated process can be carried out consistently and effectively in the tissue establishment environment by the staff.
135. Processing steps must be documented in SOPs which must conform to the validated method. The DI or LH must ensure that all processes are conducted in accordance with the approved SOPs. The processing steps must undergo regular critical evaluation to ensure that they continue to achieve the intended results.
136. Where a microbial inactivation procedure is applied to the tissue or cells, it must be specified, documented, and validated.
137. Before implementing any significant change in processing, the modified process must be validated and documented. There should be regular review and evaluation of the cumulative effects of minor changes to the processing method. Procedures for discarding tissue and cells must prevent the contamination of other donations and products, the processing environment or personnel. These procedures must comply with the HTA's [codes of practice](#).

Storage and release of products

138. The maximum storage time for tissues and cells must be specified. Where tissues and cells can be stored under different conditions and temperatures, expiry dates may need to take into account the different storage conditions. The selected period must reflect possible deterioration of the tissue and cell properties.

139. In the case of irreplaceable autologous or highly matched allogeneic tissue, use of the tissue following expiry may be permissible, based on a documented risk assessment authorised by the DI and made with clinical input.
140. A system for identification of tissues and cells throughout any phase of handling in the tissue establishment must clearly distinguish released products from non-released, quarantined and discarded products.
141. There must be an SOP that details the circumstances, responsibilities and procedures for the release of tissues and cells for distribution in accordance with these directions.
142. Records must demonstrate that before tissues and cells are released all appropriate specifications are met, in particular all current declaration forms, relevant medical records, processing records and test results have been verified according to a written procedure by a person authorised for this task by the DI. If a computer is used to release results from the laboratory, an audit trail should indicate who was given responsibility for their release by the DI.
143. A documented risk assessment approved by the DI must be undertaken to determine the fate of all stored tissues and cells following the introduction of any new donor selection or testing criterion or any significantly modified processing step that enhances safety or quality.
144. All storage processes must be carried out under controlled conditions.

Release for Circulation

145. Released for circulation means the release of tissues and cells from a TE for any purpose. This includes:
- a) transfer to another TE or third party with or without return, for example when tissues and cells are transferred elsewhere for processing; and,
 - b) distribution for human application, which is a TE releasing tissues or cells for end use.
146. A licence for distribution will only be required when tissues and cells are released for circulation for the purposes of point b in [paragraph 145](#).
147. Documented agreements must be in place that clearly define the role of each party in the transport, delivery and receipt of tissues and cells that are transferred between licensed or accredited tissue establishments within the EEA.
148. Any establishment transferring tissues or cells between different organisations, regardless whether inside the UK or outside, is required to have suitable traceability systems in place.
149. Organisations responsible for the transport and delivery of tissues or cells to any licensed or accredited tissue establishment within the EEA must adhere to the general transport requirements outlined in paragraphs [162 to 164](#)

Distribution to end users for human application

Licensing requirements

150. [The Regulations](#) require a licence for distribution whenever a person controls the provision of services for transporting or delivering tissue or cells, to anywhere in or outside of the United Kingdom, for human application.
151. This licensing requirement will apply, whenever the establishment is responsible for the distribution to the end user, regardless of whether the end user is a licensed establishment in its own right.

General requirements

152. Procedures must be in place for the handling of requests for distribution of tissues and cells. The allocation of tissue and cells to certain patients or health care institutions must be

documented and made available to these parties upon request subject to the requirements of Regulation 13 of [the Regulations](#).

153. A documented system must be in place for the handling of returned products including criteria for their acceptance into the inventory, if applicable.
154. The tissue establishment will maintain at least the following distribution data:
 - a) date of distribution;
 - b) identification of the clinician or end user/facility.
155. Distribution to end users must be in the course of agreements which ensure traceability is maintained and that serious adverse events or reactions are reported back to the tissue establishment. Agreements may be put in place on an ad hoc basis at the time of distribution.
156. Written agreements with end users should specify what traceability information should be retained by end users and for how long, and arrangements for reporting to the tissue establishment if required. Tissue establishments may consider whether traceability information may be collated and stored by the tissue establishment itself instead of the end user. However, the requirement for end users to report [serious adverse events and reactions](#) persists and this should be clearly communicated.
157. Additionally the HTA considers it desirable that a patient's notes clearly indicate if a patient has been the recipient of a human tissue or cells allograft, including acellular allografts, and distributing tissue establishments may consider advising end users to do so.
158. Where traceability information is stored by end users, it is the responsibility of the distributing establishment to put in place suitable control measures, such as feedback and audit for verifying these are in place.
159. The minimum information to be provided to the tissue establishments by end users is:
 - a) identification of the supplier tissue establishment;
 - b) identification of the clinician or end user/facility;
 - c) type of tissues and cells;
 - d) product identification;
 - e) identification of the recipient;
 - f) date of application or date of disposal;
 - g) the SEC (if applicable).
160. The HTA may authorise licensed establishments to distribute, import into the United Kingdom from a third country, or export from the United Kingdom to a third country tissues and cells directly from where the procurement takes place to an ORHA. This only applies to tissues and

cells that have been specified by the HTA in accordance with Regulation 7(4) of the Regulations and where these tissues and cells are intended for immediate human application.

161. In cases of emergency, HTA may authorise any person to distribute, import or export tissue or cells directly from where the procurement takes place to an organisation responsible for end use. These tissues and cells are exempted from the requirements of the SEC provided that traceability is assured by other means.

Transport and Packaging

162. The transport of tissues and cells must be carried out in a manner and under conditions that ensure their safety and quality at all times. In particular, the transport conditions, including temperature and time limit, must be specified and validated.
163. The shipping container must be suitable for the transport of biological materials and be able to maintain the tissues or cells in the specified conditions for safety and quality of the tissue or cells. Packaging must minimise the risk of contamination and must be able to preserve the tissue at the specified temperature for the maximum transit time that has been set. The packaging must also protect those handling or transporting the tissues and cells from potential biohazards. All containers and packages must be validated for their intended use.
164. When tissues and cells are transported by a third party, and the provision of this service could affect the quality and safety of the tissues and cells, a third party agreement should be put in place in accordance with paragraphs [227](#) onwards to ensure that the specified conditions are fulfilled. The DI must assess the need for a specific third party agreement based on the requirements for transport.

Recall

165. Each tissue establishment must ensure that an accurate, rapid and verifiable procedure is in place which will enable it to recall any product, for example following the discovery of an adverse event or reaction.
166. There must be personnel authorised within the tissue establishment to assess the need for recall and to initiate and coordinate the necessary actions.
167. The recall procedure must include a description of the responsibilities and actions to be taken. This must include [notification to the HTA](#).
168. Actions must be taken within pre-defined periods of time and must include tracing all relevant tissues and cells both back to the donor and the donation as well as to any other recipient. The purpose of the investigation is to identify any donor who might have contributed to causing the reaction in the recipient and to locate any other tissues and cells from that donor that are still

in circulation, as well as to notify consignees and recipients of tissues and cells procured from the same donor in the event that they might have been put at risk.

Labelling for distribution to end users

169. Primary tissue or cell containers must contain:
- a) type of tissues and cells, identification number or code of the tissue or cells, lot or batch number;
 - b) expiry date;
 - c) identification of the tissue establishment or distributor in the UK;
 - d) in the case of autologous donation: labelled as such and the donor/recipient has to be identified;
 - e) in the case of directed donations – the label must identify the intended recipient;
 - f) when tissues and cells are known to be positive for a relevant infectious disease marker, it must be marked as: BIOLOGICAL HAZARD;
 - g) the SEC as applicable to tissues and cells being distributed for human application.
170. If any of the information under paragraph 169 points (d) (e) and (g) above cannot be included on the primary container label, it must be provided on a separate sheet accompanying the primary container. This sheet must be packaged with the primary container in a manner that ensures that they remain together.
171. The following information must be provided either on the label or in accompanying documentation:
- a) description (definition) and, if relevant, dimensions of the tissue or cell product;
 - b) morphology and functional data where relevant;
 - c) date of distribution of the tissue or cells;
 - d) biological determinations carried out on the donor and results;
 - e) storage recommendations;
 - f) instructions for opening the container, package, and any required manipulation/reconstitution;
 - g) expiry dates after opening/manipulation;
 - h) instructions for reporting [serious adverse reactions and/or events](#);
 - i) presence of potential harmful residues (e.g. antibiotics, ethylene oxide etc.);
 - j) for imported tissues and cells, the country of procurement and the exporting country (if different from the procurement country).
172. For transport, the primary container must be placed in a shipping container that must be externally labelled with at least the following information:

- a) identification of the originating tissue establishment, including an address and phone number;
- b) identification of the organisation responsible for end use, including an address and phone number;
- c) a statement that the package contains human tissue or cells and **HANDLE WITH CARE**;
- d) where living cells are required for the function of the graft, such as stem cells, the following must be added: **DO NOT IRRADIATE**;
- e) recommended transport conditions (e.g. keep cool, in upright position, etc.);
- f) safety instructions/method of cooling (when applicable).

Traceability and Coding

173. Tissue establishments that receive and distribute tissues and cells must have a donor identification system which assigns a unique code to each donation and to each of the products associated with it.
174. All establishments must ensure that appropriate traceability of these tissues and cells is guaranteed throughout the entire chain from donation and procurement to human application.

European Coding System

175. The SEC must be made up of a the Donation Identification Sequence (SEC-DI) and a Product Identification Sequence (SEC-PI) written in the following format:
 - a) it must be eye-readable; and
 - b) it must be preceded by the letters SEC; and
 - c) it must be written as either: one line, with the SEC-DI and the SEC-PI separated by a single space; or, as two successive lines.

The Donation Identification Sequence (SEC-DI)

176. The SEC-DI must be made up of:
 - a) the ISO country code in which the allocating tissue establishment (TE) is based. This will be two alphabetic characters;
 - b) the TE number of the establishment responsible for allocating the SEC-DI. For HTA licensed establishments this will be the establishment number preceded by a zero (0); and
 - c) a unique donation number (UDN) comprising thirteen alpha-numeric characters.

The Product Identification Sequence (SEC-PI)

177. The SEC-PI must be made up of:
 - a) The Product Coding System Identifier – one alphabetic character as defined by the EU Tissue and Cell Product Compendium;
 - b) The product number – seven alpha-numeric characters as set out in the EU Tissue and Cell Product Compendium;
 - c) An appropriate split number – written as three alpha-numeric characters
 - d) The expiry date - in the format YYYYMMDD.
178. Any product code used within the SEC must already be included in the EU Tissue and Cell Product Compendium.

179. Establishments should only use the category 'other' where no other product code is available. Where this is the case, establishments should notify the HTA. If necessary the HTA will request that a new category be added to the EU Tissue and Cell Product Compendium.
180. For tissues and cells without a defined expiry date, this should be replaced within the SEC-PI by eight zeros (written as 00000000).

General Requirements relating to the SEC

181. Unless exempted, a SEC should be allocated to all tissues and cells before their distribution for human application.
182. For material imported from outside the EU, importing tissue establishments (ITE) should ensure that the SEC is applied to imported tissues and cells. This can be done by the ITE, or it can be delegated to a third country supplier (3CS) as part of the terms of a written agreement.
183. For the SEC-DI, the ITE should use the tissue establishment code allocated to it in the EU Tissue Establishment Compendium and should allocate a unique donation number if the donation number on the imported product is not globally unique.
184. Establishments are required as a minimum to allocate a SEC-DI after procuring the tissues and cells, or when receiving them from a procurement organisation, or when responsible for importing tissues and cells from a 3CS.
185. Whenever tissues and cells are released for circulation, the tissues and cells must, as a minimum, have the SEC-DI applied in accompanying documentation.
186. The SEC must be applied in full at the latest before distribution for human application, however it may be applied earlier. Establishments may also delegate application of the SEC to a third party as long as this provision is stipulated in a written agreement.
187. The SEC must be applied on the product label in an indelible and permanent manner and included in accompanying documentation.
188. Tissues and cells that are distributed for immediate transplantation, as referred to in [paragraph 160](#) may be exempt from the requirements of the SEC as set out in Article 10 (2) b of Directive 2006/86/EC (as amended).
189. Paragraph 188 does not apply to any tissues and cells that are subject to transfer to another licensed establishment by, or on behalf of the ORHA, following distribution for immediate transplantation.

Amendments to the SEC

190. After a SEC-DI has been allocated to tissues and cells released for circulation it cannot be altered. The only exception to this is when it is necessary to correct an encoding error. Such alterations require proper documentation.
191. Other amendments to the SEC may be made in accordance with a documented change control procedure that ensures that only the final version of the SEC is visible on the product label at the point of release.
192. Any changes must be properly documented, and included in all primary packaging and accompanying documentation. Changes to the primary packaging should be achieved through relabelling of the container, with the previous version of the SEC being clearly invalidated on the packaging. The new SEC must not be attached over the invalidated version of the SEC.

Allocation and Application of the SEC

193. In order to allocate the SEC, establishments must use their internal traceability system to formally assign the SEC-DI or full SEC to a unit of tissues or cells.
194. Application refers to when the SEC-DI or full SEC is physically recorded in accompanying documentation and/or on the tissue or cells label.
195. Where the size of a label is too small for the SEC to be applied in full, it may be applied in the accompanying documentation providing that it is unambiguously linked to the tissues or cells.
196. Establishments may include supplementary coding systems on the product label and incorporate the SEC into a bar code, as long as the provisions set out in [paragraph 175](#) have been fulfilled.

Tissues and cells used within the same centre

197. The SEC-DI/SEC do not need to be applied to tissues and cells providing that they remain within the same centre for all steps from procurement, or import, through to human application.
198. This exemption applies providing that all steps from procurement/import to human application are carried out under the same DI, quality management system and traceability system and where the licensed establishment and organisation responsible for human application (ORHA) are part of the same healthcare centre.
199. Within the UK, this could include where the licensed tissue establishment and the ORHA are part of the same Trust, but on different hospital sites, providing an establishment can demonstrate that there is suitable DI oversight and a single quality management system and traceability system are in place.

Tissues and cells procured prior to 1 April 2018

200. The Regulations make transitional provisions for any tissues and cells that were placed into storage in the UK prior to 1 April 2018.
201. For any tissues and cells placed into storage before 29 October 2016:
- a) products that are released for circulation before the 29 October 2021 will be exempt from the obligations relating to the SEC provided that full traceability is ensured by alternative means; or
 - b) for products that are released for circulation after 29 October 2021 and for which the application of the SEC is not possible, in particular because the tissues and cells are stored under deep-freeze conditions, the small labels exemption ([paragraph 195](#)) may be used.
202. For tissues and cells placed into storage between 29 October 2016 and 1 April 2018, that are released after 1 April 2018:
- where application of the SEC is not possible, in particular because the tissues and cells are stored under deep-freeze conditions, the small labels exemption ([paragraph 195](#)) may be used.

Traceability

203. LHs must have systems in place to ensure that all tissues and cells procured, processed, stored or distributed in the UK are traceable from donor to recipient and vice versa. Full traceability must also be in place for all products and materials coming into contact with these tissue and cells and that could have a critical impact on the quality and safety of the tissue or cells.
204. All tissues and cells must be identified with a label that contains information referred to in paragraphs [169 to 171](#).
205. Tissue establishments must keep the data necessary to ensure traceability at all times. Data required for full traceability must be kept for a minimum of 30 years after clinical use in an appropriate and readable storage medium. Data storage may also be in electronic form.
206. DIs will ensure that tissue establishments and third parties responsible for end use retain the required information. Where material has been imported into the UK, establishments must

ensure that relevant information retained abroad remains accessible for the required time (see [Import section](#)).

207. Tissue establishments must retain the following data for full traceability:

- a) donor identification;
- b) donation identification that will include at least:
 - identification of the procurement organisation or tissue establishment;
 - unique donation ID number;
 - date of procurement;
 - place of procurement;
 - type of donation (e.g. single or multi-tissue; autologous or allogeneic; living or deceased).
- c) product identification that will include at least:
 - identification of the tissue establishment;
 - type of tissue and cell/product (basic nomenclature);
 - pool number (if applicable);
 - split number (if applicable);
 - expiry date (if applicable);
 - tissue/cell status (i.e. quarantined, suitable for use etc.);
 - description and origin of the products, processing steps applied, materials and additives coming into contact with tissues and cells and having an effect on their quality and/or safety;
 - Single European Code (if applicable);
 - identification of the facility issuing the final label.
- d) human application identification that will include at least:
 - date of distribution or disposal;
 - identification of the clinician or end user/facility.

208. It is further the responsibility of the DI to have agreements in place that either:

- a) put systems in place to obtain the end use information required in paragraph [159](#); or
- b) ensure that end users have systems in place to retain the information required in paragraph [159](#) for the required time and keep it accessible.

If option b is applied the DI must conduct regular audits of traceability with end users.

209. Distributors of imported material must have agreements in place that ensure that the information required in paragraph [207 a to c](#) is held at the overseas exporter/ tissue bank for the required time.

Serious adverse events and reactions

210. Licensed establishments must have a system in place for reporting, investigating, registering and recording information about serious adverse events (SAEs) and reactions (SARs) which may influence the quality and safety of tissues and cells and which may be associated with any licensable activity, as well as any SAR observed during or after clinical application which may be linked to the quality and safety of tissues and cells.
211. The above system must ensure that:
- c) staff responsibilities for the management of SAEs and SARs are clearly defined;
 - d) immediate actions can be taken to ensure damage limitation, including:
 - effective use of traceability information to ensure all tissues and cells related to a particular donor or donation can be identified;
 - [recall](#);
 - notification of other establishments;
 - where necessary, the temporary cessation of licensable activities implicated in the SAE/SAR.
212. There must be systems and procedures for communication with other organisations affected or implicated in the SAE/SAR, such as other licensed establishments, third parties and suppliers of critical goods and services.
213. A thorough root cause analysis must be undertaken in a timely manner, which includes the identification of individuals and processes which might have contributed to the SAE or SAR.
214. Corrective and preventative actions must be implemented which address the problems identified and do not adversely affect other systems. Implementation should be signed-off on completion.
215. All records associated with the SAE or SAR must be retained.
216. It is the responsibility of the DI to ensure that the HTA is notified of any SAE or SAR via the HTA's online submission system. This responsibility may be delegated in circumstances where the DI is unavailable and in the interests of timely reporting, however the DI retains overall responsibility for ensuring that such notifications and reports are received by the HTA.
217. The initial notification to the HTA should be given within 24 hours of the discovery or determination of the SAE or SAR by the licensed establishment. Third parties and end users should be instructed to report to the licensed establishment within 24 hours of their discovery of SAEs or SARs. Tissue establishments should be able to respond to SAEs and SARs within this time frame inside their normal operational hours.

218. The tissue establishment must notify the HTA of the actions taken with respect to other implicated tissues and cells that have been distributed for human applications.
219. A follow-up report must be provided to the HTA within 90 days, which outlines the root cause analysis and the corrective and preventative actions indicated to prevent recurrence.
220. Following notification of any SAE or SAR, the HTA may organise an inspection of the licensed establishment, or any relevant third party premises, and can require the establishment to carry out such control measures as are deemed appropriate.
221. The HTA may also carry out an inspection and require control measures to be carried out at the request of another Competent Authority

SAEs and SARs detected by end users

222. All end users must report any relevant information to establishments responsible for the release and distribution of human tissues and cells in order to facilitate traceability and ensure quality and safety control. This requirement should be included in any written agreement between tissue establishments and end users.
223. End users must have procedures in place to retain the records of tissues and cells applied and to notify the supplying tissue establishment within 24 hours of any SAR observed during and after clinical application and any SAE which may be linked to the quality and safety of tissues and cells
224. Tissue establishments that distribute tissue and cells for end use must provide information to end users about how that organisation should report SAEs and SARs. This requirement should also form part of any written agreement between the tissue establishment and the end user, or the terms and conditions of the supply agreement. Whichever form the agreement takes, the reporting obligation must be highlighted to the end users.

SAE and SARs during procurement

225. Licensed procurement organisations must have procedures in place to retain the records and to notify the HTA and any implicated tissue establishments within 24 hours of any SAR affecting a living donor and of any SAE or SAR that occur during procurement and which may influence the quality or safety of the tissues and/or cells.
226. Procurement organisations acting under a TPA with a licensed tissue establishment must have procedures in place to ensure the requirements of paragraph 225 can be met.

Third party agreements

227. Third party agreements (TPAs) must be put in place whenever an unlicensed third party in the UK carries out **licensable activities** (procurement, testing, processing, distribution or export) on behalf of a licensed establishment. The establishment must itself be licensed for that activity.
228. It is not possible to carry out storage or import under a TPA.
229. [The Regulations](#) also require a third party agreement where the third party provides or supplies **goods or services that affect quality or safety of the tissues or cells**.
230. The establishment must evaluate and select third parties on the basis of their ability to meet the requirements of their own licence.
231. The HTA does not require that any establishment has a third party agreement with its own staff (i.e. persons who are employed by the establishment as members of staff).

Third Parties carrying out licensable activities

232. Licensed establishments must inform the HTA of all third parties carrying out **licensable activities** on behalf of the establishment under third party agreements, prior to commencement of these activities. Written documentation must be provided to demonstrate the suitability of the third party and compliance with the licensing standards. Evidence may consist of the agreed procedures, other accreditations of the third party and the control measures that the licensed establishment is implementing.
233. No licensable activities may be carried out by the third party until the HTA is satisfied that the proposed relevant third party and any relevant third party premises are suitable.
234. If a third party carries out any processing steps on behalf of a licensed establishment, the DI should be satisfied that the provider's procedures can be integrated into the establishment's quality system. In case of other licensable activities this requirement needs to be evaluated on a case by case basis.
235. The DI must be able to demonstrate that sufficient control measures are in place to ensure that the licensable activities are carried out by the third party in accordance with HTA licensing standards and this guide. In the case of processing, this will always include regular full audits of the entire service carried out independently by the DI at least at two yearly intervals.

Third parties supplying goods or services

236. Sales contracts with suppliers of standardized critical materials, reagents or services (e.g. blood bags, off-the shelf reagents) are normally considered sufficient to satisfy the requirement for third party agreements, in particular where the product is CE marked and has a certificate of analysis. Licensed establishments should have a list of their approved suppliers of such critical goods and services.
237. Where more customised reagents, materials or services are provided (e.g. material provided solely to an individual licensed establishment as per their specification) more detailed third party agreements may be required. The list of approved suppliers must indicate with whom individual third party agreements have been put in place.

Content of third party agreements

238. The HTA has produced a template document for use by licensed establishments and third parties, to cover licensable activities and individual TPAs in relation to goods or services as defined in paragraph 236. The draft template can be found in [Annex C](#) together with more detailed guidance on the legal requirements.
239. Where the establishment and the third party are independent entities which enter into a contract for the carrying on of a licensed activity, the third party agreement must contain the following:
- a) agreements with third parties must specify the terms of the relationship and responsibilities as well as the protocols to be followed to meet the required performance specification;
 - b) the establishment must ensure that the following core requirements are included in each third party agreement:

- i. full address and contact details of the third party, and nature of the service to be provided;
 - ii. identification of person(s) responsible for managing arrangements between the centre and the third party;
 - iii. provision setting out how often the agreement will be reviewed and by whom;
 - iv. summary of the responsibilities of the third party and agreed procedures with regard to each party's respective responsibilities;
 - v. any specific criteria that the service provided by the third party must meet, particularly in relation to quality and safety;
 - vi. description of how any test/diagnostic results are relayed to the commissioning centre, including sign off and confirmation that the result applies to the correct sample;
 - vii. ensure that adverse incidents are reported and that any affected tissues or cells can be effectively recalled;
 - viii. agreement that the third party will meet the requirements of the licence held by the establishment for the carrying on of the detailed activity.
- c) Where the third party procures tissues or cells on behalf of an establishment, the third party agreement must require the procuring establishment to produce a report to the licensed establishment which must include a record of the following:
- i) where the procurement took place;
 - ii) patient/donor identification data including how and by whom identified;
 - iii) description and identification of the procured tissue or cells including samples for testing;
 - iv) identification of the person responsible for the procurement process;
 - v) date, time and location of procurement and SOP used;
 - vi) details of any incidents, including any serious adverse events and/or reactions, that occurred during the procurement process;
 - vii) where appropriate, the environmental conditions at the procurement facility; and
 - viii) where appropriate, the identification/batch numbers for any reagents and transport media used.
240. The establishment must keep a complete list of agreements that they have established with third parties. Copies of these agreements must be made available to the Authority upon request.

HTA's powers in relation to third party agreements

241. The HTA has powers to enter and inspect third party premises.
242. The HTA has powers to direct a licensed establishment to put in place a TPA with a supplier of goods or services where it considers this necessary. The HTA equally has powers to direct an individual licensed establishment not to use a named supplier of either goods or

services. Under extreme circumstances the HTA may give details of suppliers from whom no licensed establishment may receive goods or services.

Import

243. Import of tissues or cells intended for human application into the United Kingdom from an EEA state or Gibraltar is not a licensable activity, however such imports must only be carried out from:
- a) a TE which is accredited, designated, authorised or licensed under the laws or other measures adopted to implement the EUTCD; or
 - b) A person who is approved to procure those tissues and cells under the laws or other measures adopted to implement the EUTCD; or
 - c) Following the procurement of tissues and cells in conditions accredited, designated, authorised or licensed under the laws or measures adopted for the purposes of implementing the EUTCD.
244. Licensed establishments that import tissues and cells from countries that are not EEA states or Gibraltar are responsible for ensuring that they meet standards of quality and safety equivalent to those set out in this document.
245. Import of tissues and cells from countries which are not EEA states or Gibraltar is a licensable activity, and can only be undertaken by establishments licensed for import by the HTA. The only exception to this is where an import has been authorised by the HTA as set out in paragraphs [160-161](#).
246. Any organisation that is responsible for ensuring the quality and safety of the imported tissues and cells (unless exempted under Regulation 7, as referred to in paragraph 245) will be required to hold an import licence under the Regulations. This includes:
- a) organisations responsible for human application,
 - b) manufacturers of ATMPs,
 - c) clinical practitioners or individuals that are a party to a contractual agreement with a 3CS for the import of tissues and cells,
 - d) an organisation offering brokerage services that is party to a contract with a 3CS and has responsibility for verifying the quality and safety of the tissues and cells
247. Tissue banks or units of hospitals will be considered to be ITE where they are a party to a contractual agreement with a third country supplier for the import of tissues and cells.
248. In accordance with standard licence condition 18, ITE will only be licensed to carry out the import of cells from outside of the EU under the terms specified in an ITE licence certificate. The ITE licence certificate will be appended as Annex E of each ITE's licence certificate.

249. Imported tissues and cells must be traceable from donor to recipient and vice versa in accordance with the traceability requirements set out in this document and agreements with the suppliers must ensure tissues and cells remain traceable for 30 years.
250. The provisions for consent set out in this document are not applicable to imported tissues and cells. Importers should satisfy themselves that consent is part of the process within the source country by which the tissues and cells are obtained.
251. With the exception of imports authorised by the HTA in accordance with Regulation 7(4) or Regulation 7(5), all imports of tissues and cells from third countries must be undertaken by a licensed ITE.

Written documentation

252. Written documentation and agreements are key elements in ensuring that verification of equivalent standards of quality and safety takes place and in particular in providing traceability back to the donor.
253. ITE must provide information on each imported tissue, cell and product type, the location where each activity takes place prior to import and information on who carried out each activity, name and contact details of each 3CS and the path that the tissues and cells take prior to import.
254. ITE must have documents which cover the following:
 - a) Documentation relating to the ITE
 - i. A copy of the primary label, repackage label, external package and transport container;
 - ii. A list of relevant and up-to-date versions of standard operating procedures (SOPs) relating to the establishment's import activities including SOPs on applying the Single European Code, reception and storage of imported tissues and cells at the ITE, management of adverse events and reactions, management of recalls and traceability from donor to recipient.
 - b) Documentation relating to the third country supplier or suppliers
 - i. A detailed description of the criteria used for donor identification and evaluation, information provided to the donor or donor family, how consent is obtained from the donor or donor family and whether the donation was voluntary and unpaid or not;
 - ii. Detailed information on the testing centre(s) used by third country suppliers and the tests performed by such centres;
 - iii. Detailed information on the methods used during the processing of the tissues and cells including details of the validation for the critical processing procedure;

- iv. A detailed description of the facilities, critical equipment and materials and criteria used for quality control and control of the environment for each activity carried out by the third country supplier;
- v. Detailed information on the conditions for release of tissues and cells by the third country supplier or suppliers;
- vi. Details of any sub-contractors used by the third country suppliers including the name, location and activity undertaken;
- vii. A summary of the most recent inspection of the third country supplier by the third country competent authority or authorities including the date of the inspection, type of inspection and main conclusions;
- viii. A summary of the most recent audit of the third country supplier carried out by, or on behalf of, the importing tissue establishment;
- ix. Any relevant national or international accreditation.

255. ITE are required to hold a written agreement with any third country supplier for the import of tissues and cells. These contracts must contain, as a minimum, the provisions set out in Annex IV of Directive (EU) 2015/566, as follows:

- a) Detailed information on the specifications of the importing tissue establishment aimed at ensuring that the quality and safety standards laid down in this document are met and the mutually agreed roles and responsibilities of both parties in ensuring that imported tissues and cells are of equivalent standards of quality and safety;
- b) A clause ensuring that the third country supplier provides the information set out in Paragraph 254 (b) above, to the ITE;
- c) A clause ensuring that the third country supplier informs the importing tissue establishment of any suspected or actual serious adverse events or reactions which may influence the quality and safety of tissues and cells imported or to be imported by the importing tissue establishment;
- d) A clause ensuring that the third country supplier informs the importing tissue establishment of any substantial changes to its activities, including any revocation or suspension, in part or in full, of its authorisation to export tissue and cells or other such decisions of non-compliance by the third country competent authority or authorities, which may influence the quality and safety of tissues and cells imported or to be imported by the importing tissue establishment;
- e) A clause guaranteeing the competent authority or authorities the right to inspect the activities of the third country supplier, including on-site inspections, should it wish to do so as part of its inspection of the importing tissue establishment. The clause should also guarantee the importing tissue establishment the right to regularly audit its third country supplier;
- f) The agreed conditions to be met for the transport of tissues and cells between the third country supplier and importing tissue establishment;
- g) A clause ensuring that donor records relating to imported tissues and cells are kept by the third country supplier or its sub-contractor, in line with EU data protection rules, for

30 years following procurement and that suitable provision is made for their retention should the third country supplier cease to operate;

- h) Provisions for the regular review and, where necessary, revision of the written agreement including in order to reflect any changes in the requirements of the EU quality and safety standards laid out in this document;
- i) A list of all standard operating procedures of the third country supplier relating to the quality and safety of imported tissues and cells and a commitment to provide these on request.

One off imports

- 256. ITE that wish to perform one-off imports will need to submit an application to the HTA in advance of any such import being carried out.
- 257. An ITE is only permitted to perform one-off imports under the terms specified in its Importing Tissue Establishment Licence Certificate.
- 258. A one-off import is the import of any specific type of tissue or cell for the personal use of an intended recipient, known to the importing tissue establishment and the third country supplier before importation.
- 259. One-off imports should not as a general rule be carried out on a regular or repeated basis for the same 3CS and should only be carried out once for any given recipient unless:
 - a. the tissues and cells imported are the same as those previously imported and are to be used for further treatment (for example in the case of disease relapse); or
 - b. there was a quality and safety issue with a previous import of the same tissue and cell type which means a further import is required; or
 - c. it is desirable to import batches of the tissues or cells in multiple shipments in order to protect against the risk of damage in transit.
- 260. The documentary requirements set out in paragraphs [254 and 255](#) will not apply to one-off imports, providing that the ITE has suitable measures in place to ensure equivalent standards of quality and safety to those set out in this document. In particular traceability from donor to recipient must be maintained and imported tissues and cells are not applied to anyone other than their intended recipients.

Notification of changes to import activities

- 261. Importing tissue establishments must seek the prior written approval of the HTA for any planned substantial changes to their import licence, and in particular the following substantial changes:

- a) Any changes to the type of tissues and cells imported;
 - b) The activities undertaken in third countries which may have an impact on the quality and safety of imported tissues and cells;
 - c) Change to the third country suppliers used.
262. Point 261 (c) does not apply where an ITE carries out a one-off import from a new 3CS, providing that the ITE holds an ITE licence certificate which permits it to carry out imports of that tissue type from another 3CS and to carry out one-off imports of that tissue or cell type.
263. ITE must inform the HTA if they decide to cease their import activities in part or in full.
264. ITE are required to notify the HTA, without delay, of
- a) Any revocation or suspension, in part or in full, of a third country supplier's authorisation to export tissues and cells; and
 - b) Any other decision taken for reasons of non-compliance by the competent authority of the country in which the third country supplier is based and which may be relevant to the quality and safety of imported tissues and cells.

Export

265. Export of tissues and cells to a third country is a licensable activity, and therefore all exports of tissues and cells to such countries can only be undertaken by establishments licensed for export by the HTA.

266. Exported tissues and cells must comply with the requirements of this document.

Termination of activities

267. The establishment must have agreements and procedures in place to ensure that, in the event of termination of activities for whatever reason (including closure of the establishment or a third party establishment), stored tissues and cells are transferred to other establishment(s) licensed for storage for human application.
268. All agreements in relation to the termination of the licensed activity (termination agreements) must, as a minimum, comply with the following:
- a) include an obligation to ensure that tissues and cells are transferred without delay to another licensed establishment following termination of activities;
 - b) include the procedures to be adopted with respect to traceability data and material concerning the quality and safety of tissues and cells;
 - c) include provision to secure that all records, including raw data, critical to safety and quality, be retained and maintained, including the transfer of such records and raw data to another licensed establishment;
 - d) include acknowledgement of the subsisting duty of the DI and/or third party, including former DIs and third parties;
 - e) include provision for the transfer of any third party agreements to another licensed establishment following termination of activities;
 - f) include provision to secure compliance with the duty of the DI and/or third party, including former DIs and third parties, regarding the disclosure of information and confidentiality;
 - g) prior to the transfer of tissues and cells, the establishment and/or any third party, must carry out an audit of stored tissues and cells and must ensure that all discrepancies are resolved. The establishment must provide a copy of the report of the audit to both the establishment to which the tissues and cells are being transferred and the HTA;
 - h) the establishment must ensure that the transfer of tissues and cells is carried out under conditions that ensure that the integrity and quality of the tissues and cells are maintained.
269. The establishment must inform the HTA if the termination of activities is planned and the details thereof (including closure of the establishment or a third party establishment). The DI and LH must provide information about the transfer of tissues, cells and records to other licensed establishments and timelines for such transfers. Relevant contact information must be provided to the HTA and to receiving establishments.
270. The establishment or any third party must complete the HTA's Closure Pro Forma which is available on request from the HTA.

Annex A – Selection criteria for donors

Annex I Commission Directive 2006/17/EC: Selection criteria for donors of tissues and/or cells (except donors of reproductive cells)

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-Jakob 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 B, 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) that may be sufficient in themselves to exclude the donor or which must be assessed in the light of the donor's medical and personal history.

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 - Laboratory tests required for donors

Annex II of Commission Directive 2006/17/EC (as amended by 2012/39/EU): 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-prevalence 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 A, point 2.1.1, applies, in that 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. 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: Guidance template for TPAs

This guidance template must be used in conjunction with the information provided in the section on [third party agreements](#).

Name of licensed establishment:

Address:

HTA licence number:

Designated Individual:

Name of third party:

Address:

Designated Contact person:

Name of person responsible for managing arrangements of the third party agreement:

Address:

Third Party Agreement covers

EITHER:

licensable activity

- Procurement
- Testing
- Processing
- Distribution
- Export

OR

- Supplies goods or services that affect quality or safety

Description of the activity:

Please attach the contract between the licensed establishment and the third party (unless the TPA is made part of the main contract)

Reference to protocols and SOPs to be followed to meet the required performance specification (attach copies)

Where applicable, reference to control measures or audits to be carried out by the licensed establishment and which the Third Party agrees to support (e.g. on site audit at specified intervals, audit of reports to be provided by third party etc.)

Reference to reporting requirements of the Third Party to the licensed establishment

Reference to systems for managing adverse events and incidents

Date on which the agreement will be reviewed:

Details of the person with responsibility to review the agreement:

We confirm that the licensed establishment and the third party are independent entities which have entered into a contract for the carrying of the licensed activity described above.

The licensed establishment confirms that it has evaluated and selected the third party on the basis of their ability to meet the

requirements of the HTA licence and the Guide to quality and safety assurance for human tissues and cells for patient treatment (for licensable activity only)

The licensed establishment confirms that it has considered whether there are any specific criteria that the third party is required to meet in relation to quality and safety.

The third party confirms that it is able to meet the requirements of the HTA licence in relation to the described activity.

Are any tests or diagnostic results sent by the third party to the licensed establishment? Yes/No

Yes- the licensed establishment confirms that it has a system to ensure sign off and confirmation that the result applies to the correct sample.

Does the third party procure tissues or cells on behalf of an establishment? Yes/No

Yes- the third party confirms it will produce a report to the licensed establishment to include:

- a) where the procurement took place
- b) patient/donor identification data including how and by whom identified
- c) description and identification of the procured tissue or cells including samples for testing
- d) identification of the person responsible for the procurement process
- e) date, time and location of procurement and Standard Operating Procedure used
- f) details of any incidents, including any serious adverse events and/or reactions, that occurred during the procurement process
- g) where appropriate, the environmental conditions at the procurement facility, and
- h) where appropriate, the identification/batch numbers for any reagents and transport media used.

Yes- the licensed establishment confirms that it is satisfied that the third party procedures are integrated with the licensed establishment's quality system.

Signed: Licensed establishment

Date:

Signed: Third party:

Date:

Copy sent to HTA on date: