

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

**Directions on the requirements of the
Human Tissue (Quality and Safety for
Human Application) Regulations 2007,
on the Standards required under the
Parent Directive, the First
Commission Directive 2006/17/EC and
the Second Commission Directive
2006/86/EC and amendments to
Directions 001/2006.**

Ref 002/2007

These Directions are

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

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| <p>Section of the Human Tissue Act 2004 (HT Act) and Regulation under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (the Regulations) providing for these Directions</p> | <p>Section 23 (1) and paragraph 2 (4) (c) to (e) of Schedule 3 of the HT Act and Regulation 15, 16 (1) and (2) and Schedule 2 of the Regulations</p> |
| <p>These Directions come into force on</p> | <p>5 July 2007</p> |
| <p>These Directions remain in force</p> | <p>Until revoked</p> |

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General

1. These Directions are made for the purposes of securing compliance with the requirements of Directive 2004/23/EC of the European Parliament and Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (hereafter “the parent directive”), Commission Directive 2006/17/EC of 8 February 2006 specifying the technical requirements for the donation, procurement and testing of human tissues and cells (hereafter “the First Commission Directive”) and Commission Directive 2006/86/EC of 24 October 2006 setting out the traceability requirements, requirements for the notification of serious adverse reactions and events and specifying the technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells (hereafter “the Second Commission Directive”) in accordance with Regulation 15 (1) and 16 (1) and (2) of the Regulations.
2. These Directions supplement, and in part, amend the Directions given under the HT Act, reference number 001/2006 and should be read with those Directions. Where there is a conflict between the provisions of these Directions and Directions 001/2006, then, except as otherwise provided in these Directions, these Directions will apply.
3. These Directions are made under section 23 (1) of the HT Act in order to comply with the Regulations and set out and clarify the obligations on establishments arising out of the Regulations. These Directions are also made for the purposes of paragraph 2 (4) (c) to (e) of Schedule 3 of the HT Act regarding the recording of information in relation to the carrying-on of the licensed activity, the period of retention of such records and the provision of records to the Human Tissue Authority (HTA) or a person authorised on behalf of the HTA.
4. References to linking or linked paragraphs are included in these Directions to facilitate persons using these Directions and do not form part of the Directions.

Interpretation and amendments to Directions 001/2006

5. The parent directive, the First Commission Directive and the Second Commission Directive (hereafter collectively referred to as “the Directives”) have been brought into UK law by way of the Regulations. This necessitates certain amendments to Directions 001/2006 and the manner in which the HTA will license activities covered by the ambit of the Directives.

Directions 001/2006 should be read in light of the following matters of interpretation which arise out of the Regulations: –

- a. References to the parent directive, the First Commission Directive, the Second Commission Directive or the Directives should now be read as referring to the relevant Directive and Directives as transposed into UK Law by the Regulations.
- b. References to third countries in Directions 001/2006 should now be read as references to states that are not members of the European Economic Area (“EEA”). For the purposes of the Regulations, these Directions and Directions 001/2006, Gibraltar is to be considered a member of the EEA. Any references in Directions 001/2006 to EU member states should now be read as references to member states of the EU, member states of the EEA and Gibraltar (hereafter “EEA member states”).
- c. Where Directions 001/2006 impose an obligation or obligations on the establishment, then that obligation or those obligations should also be read as included in the duty of the Licence Holder (LH) on behalf of the establishment and / or the duty of the Designated Individual (DI) on behalf of the establishment.
- d. Annex C (Definitions) of Directions 001/2006 is hereby replaced by Annex C of these Directions. Directions 001/2006 shall be read as if the definitions contained in Annex C of these Directions were substituted for Annex C of Directions 001/2006 and those Directions shall be read accordingly.
- e. Paragraph 3 of Directions 001/2006 shall be read with and is amended by paragraph **9** below.
- f. The HTA is regulating establishments involved in the donation, procurement, testing, processing, preservation, distribution and import or export of tissues and / or cells for human application in accordance with paragraph **14** below. That paragraph will replace paragraph 10 of Directions 001/2006.
- g. References to the period of thirty years in paragraphs 24 and 55 of Directions 001/2006 shall be read as if the following was inserted immediately after the words “thirty years”: “(or such longer period as may be specified by the HTA in Directions)”.

- h. References to agreements between tissue establishments and third parties in Directions 001/2006 should now be read as references to third party agreements made in accordance with paragraph **117** below. Paragraphs 4(j), 66 and 68 to 70 of Directions 001/2006 must accordingly be read with, and are hereby amended by, paragraphs **117**, **118** and **119** below.
- i. Paragraph 71 of Directions 001/2006 is hereby amended by addition of the following words after the word “activities”:
 - “or activity or activities carried out under a third party agreement made in accordance with Directions 002/2007.
- j. Reference to third parties in paragraph 17 of Directions 001/2006 should now be read as including, but not limited to, a third party as defined in these Directions.
- k. References to Service Level Agreements (SLAs), contracts and / or documented agreements between tissue establishments and third parties including procuring establishments in paragraphs 6, 34 and 41 of Directions 001/2006 should now be read as references to third party agreements made in accordance with paragraph **117** below.
- l. Reference to SLAs in paragraph 15 of Directions 001/2006 should now be read as a reference to third party agreements made in accordance with paragraph **117** below, where appropriate.
- m. The requirements for labelling of the shipping container set out in paragraph 41 of Directions 001/2006 apply where tissues and / or cells are being transported prior to distribution to end users. The requirements for final labelling for distribution, whether by the establishment or a third party distributing on behalf of the LH are as set out in these Directions.
- n. Paragraph 64 (a) of Directions 001/2006 is hereby amended by addition of the following words after the word “purpose”: – “or in respect of which there exists a third party agreement between the LH, or the DI on behalf of the LH, and the establishment from which the tissues and / or cells are imported in accordance with these Directions as amended by Directions 002/2007”.
- o. Directions 001/2006 shall from the 5 July 2007 be deemed to be Directions given under the HT Act for the purposes of implementing the Regulations and under paragraph 2 (4) (c) to (e) of Schedule 3 of the HT Act.

6. Except as otherwise provided in Annex C of these Directions, words and expressions used in these Directions shall have the same meaning as in Article 3 of the parent directive, Article 1 of the First Commission Directive and Article 2 of the Second Commission Directive.
7. References in these Directions and Directions 001/2006 to “storage” means maintaining tissue or cells, whether by preservation or in any other way, for more than 48 hours. The words “store” and “stored” are to be interpreted accordingly.

Licence Holder

8. The LH shall have responsibility for: –
 - a. Entering into agreements with third parties (hereafter “third party agreements”) on behalf of the establishment under which the third party:
 - i. procures, tests, processes, distributes, imports or exports tissues and / or cells on behalf of the LH; or
 - ii. supplies to the LH any goods or services which may affect the quality or safety of tissues and / or cells,

and which complies with the requirements set out in accordance with paragraphs **118** and **119** below. The LH may delegate the entering into of third party agreements to the DI but will nonetheless retain responsibility for ensuring that third party agreements comply with the requirements of these Directions in accordance with paragraphs **118** and **119** below. This is subject to the DI’s statutory duty to secure that the conditions of third party agreements are complied with in accordance with paragraph **11** below;
 - b. Ensuring, in conjunction with the DI, that third party agreements are maintained in accordance with the requirements of the Regulations and these Directions and that appropriate standard operating procedures (SOPs) are in place and complied with in accordance with paragraph **14(c)** below.
 - c. Ensuring that the requirements for the licensing of tissue establishments as laid down in Annex I of the Second Commission Directive are complied with in accordance with paragraphs **15** to **48** below;

- d. Ensuring that any third party, with whom the LH, or the DI on behalf of the LH, has a third party agreement established in accordance with paragraph **117 (a)** below, and paragraph **117 (b)** below, where appropriate, has a documented system that ensures the identification of every unit of tissue and / or cells at all stages of the activity or activities carried out by the third party on behalf of the LH in accordance with paragraph **25** below;
- e. Ensuring that the requirements for the authorisation of tissue and cell preparation processes, as set down in Annex II of the Second Commission Directive, are complied with in accordance with paragraphs **49** to **56** below;
- f. Ensuring that any information collected in pursuance of a licence or a third party agreement and from which a donor, whether living or deceased, or recipient of tissues and / or cells may be identified and which is disclosed to the LH for the purposes of his / her functions under the licence, is kept confidential and not disclosed other than in circumstances permitted by law in accordance with paragraph **63** below;
- g. Making any necessary application to the HTA for approval for direct distribution of specified tissues and / or cells from where the procurement takes place to an organisation responsible for human application for immediate human application in accordance with paragraph **69** below;
- h. Ensuring, in conjunction with the DI, that the establishment and third parties responsible for human application retain the minimum donor / recipient data and the information contained in the European coding system to secure compliance with the information requirements of the Second Commission Directive and in accordance with paragraphs **70, 71, 82 83, and 84** below;
- i. Ensuring that the establishment adopts such systems as the HTA considers appropriate to secure compliance with the traceability and coding provisions of the parent directive and the Second Commission Directive and in accordance with paragraphs **79** to **86** below;
- j. Ensuring that any third party, with whom the LH, or the DI on behalf of the LH, has a third party agreement established in accordance with paragraph **117 (a)** below, has effective and accurate systems to identify and label tissues and / or cells to secure compliance with the

traceability and coding provisions of the parent directive, the First Commission Directive and the Second Commission Directive and in accordance with paragraph **80** below;

- k. Ensuring that the establishment adopts the necessary systems to report, investigate, register and transmit information about serious adverse events and / or serious adverse reactions, has accurate, rapid and verifiable procedures for the recall of products related to serious adverse events and / or serious adverse reactions and has the necessary procedures to retain records and comply with the notification requirements in relation to serious adverse events and / or serious adverse reactions in compliance with the parent directive and the Second Commission Directive and in accordance with paragraphs **98** to **101** and **106** below;
- l. Ensuring that procurement organisations and organisations responsible for human application have the necessary procedures to retain records of tissues and / or cells procured and / or applied and to comply with the notification requirements in relation to serious adverse events and / or serious adverse reactions as set out in the Second Commission Directive and in accordance with paragraph **98** below;
- m. Ensuring, in conjunction with the DI, that any third party, with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph **117** below, establishes and maintains an accurate, rapid and verifiable recall procedure which complies with the provisions of these Directions, as amended from time to time in accordance with paragraph **107** below;
- n. Making any necessary application to the HTA for approval for the import or export of specified tissues and / or cells from where the procurement takes place to an organisation responsible for human application for immediate human application in accordance with paragraph **109** below;
- o. Making any necessary application to the HTA for approval for the distribution of specified tissues and / or cells from where the procurement takes place to an organisation responsible for human application for immediate human application in accordance with paragraph **110** below;
- p. Ensuring, in conjunction with the DI, that all imports of human tissues and / or cells from non EEA states meet

standards of quality and safety equivalent to those set down in the Regulations, the Directives and as set out in Directions given by the HTA from time to time and in accordance with paragraph 111 below;

- q. Ensuring that procurement organisations comply with the minimum information to be furnished on donation in accordance with Article 13 (2) and the Annex to the parent directive and as set out in paragraph 14 of Directions 001/2006;
- r. Ensuring, where their licence authorises procurement, that the requirements for the procurement of human tissues and / or cells laid down in the First Commission Directive and as set out in paragraphs 25 to 32 and 43 to 47 of Directions 001/2006 are complied with; and
- s. Ensuring that the selection, evaluation and procurement of human tissues and / or cells intended for human application and the reception of human tissues and / or cells at the establishment are carried out in compliance with the parent directive and the First Commission Directive and as more specifically set out in paragraphs 26 to 32 and 43 to 47 of Directions 001/2006.

Designated Individual

- 9. The minimum qualifications, which the DI must possess, are set out in paragraph 3 of Directions 001/2006. The two years' practical experience required by paragraph 3 (b) of those Directions must be experience, which is directly relevant to the activity or activities authorised by the licence.
- 10. Where the DI does not have a medical or biological qualification, then the DI must have access to a nominated registered medical practitioner and / or a scientific adviser, as the HTA considers appropriate, to assist the DI and provide advice and guidance in relation to clinical and scientific activities. The role of the nominated registered medical practitioner and / or scientific adviser will be in accordance with paragraph 17 below.
- 11. In addition to the responsibilities set out in Directions 001/2006 at paragraph 4, 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 activity or activities;

- b. suitable practices are used in the course of carrying out the licensed activity or activities;
 - c. the conditions of the licence are complied with;
 - d. the conditions of third party agreements in relation to the licensed activity or activities authorised to be carried out under his supervision are complied with; and
 - e. the requirements of Regulation 13(1) (Information and Confidentiality) are complied with.
12. In addition to the responsibilities set out in Directions 001/2006 at paragraph 4 and the statutory duty referred to in paragraph 11 above, the DI shall have responsibility for: –
- a. Notifying the HTA of suspected serious adverse events and suspected serious adverse reactions without delay and in any event within such timeframe (if any) as the HTA may specify in Directions. Such notification must contain the information required in accordance with paragraph **101** below and Annexes **A** and **B** to these Directions and shall be in an approved format in accordance with paragraph **100 (e)** below;
 - b. Providing the HTA with a report of the conclusions of the serious adverse events and / or serious adverse reactions investigation without delay and within such timeframe as the HTA may specify in Directions. Such report must contain the information required in accordance with paragraph **100 (e)** below and Annexes **A** and **B** to these Directions and shall be in an approved format in accordance with paragraph 100 below;
 - c. Ensuring, in conjunction with the LH, that third party agreements are maintained in accordance with the requirements of the Regulations and these Directions and that appropriate SOPs are in place and complied with in accordance with paragraph **14(c)** below.
 - d. Supervising the establishment's documented system for ratifying that tissues and / or cells intended for human application meet appropriate specifications for safety and quality for release and for their distribution in accordance with paragraph **23** below;
 - e. Ensuring that all personnel are suitably qualified for the tasks they perform and that their competency is evaluated in accordance with paragraphs **26** and **27** below;

- f. Ensuring that all personnel are provided with the necessary initial and updated training to carry out the tasks that they perform and that the training programme provided is in accordance with paragraph **28** below;
- g. Ensuring that all personnel are provided with the necessary training including access to continuing and professional development programmes in accordance with paragraph **29** below;
- h. Ensuring that the equipment and materials used at the establishment are fit for purpose and that they are selected, maintained, and used in accordance with paragraph **33** below;
- i. Ensuring that the equipment and materials used by any third party, with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph **117 (a)** below, and paragraph **117(b)** below, where appropriate, are fit for purpose and that they are selected, maintained, and used in accordance with paragraph **33** below;
- j. Ensuring that the premises and facilities at the establishment are suitable for the activity or activities for which it is licensed and are provided and maintained in accordance with paragraphs **36–43** below;
- k. Ensuring that relevant third party premises and the facilities of any third party, with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph **117 (a)** below, and paragraph **117 (b)** below, where appropriate, are suitable for the activity or activities carried out by the third party on behalf of the LH and are provided and maintained in accordance with paragraphs **36–43** below;
- l. Ensuring that the establishment has and maintains appropriate staff facilities at all times and that staff are provided with appropriate garments and equipment for personal protection and hygiene, together with instructions for their use in accordance with paragraph **44** below;
- m. Ensuring that the establishment maintains the documentation and records required to ensure compliance with the parent directive, the First Commission Directive and the Second Commission Directive including those required in accordance with paragraph **45** below;

- n. Ensuring that the establishment puts in place, maintains and updates an audit system and system of quality review in accordance with paragraphs **47–48** below;
- o. Ensuring that he / she participates in regular and continuing education and professional development programmes and in particular when procedures change or scientific knowledge develops;
- p. Approving the documented risk assessment to be undertaken to determine the fate of all stored tissues and / or cells following the introduction of any new donor selection or testing criterion or any significantly modified processing step in accordance with paragraph **51 (e)** below;
- q. Ensuring that all information which is collected in pursuance of the licence or a third party agreement is kept confidential and only disclosed in circumstances permitted by law, is maintained, made available and held in accordance with paragraph **60** below;
- r. Ensuring, in conjunction with the LH, that the establishment and third parties responsible for human application retain the minimum donor / recipient data and the information contained in the European coding system to secure compliance with the information requirements of the Second Commission Directive and in accordance with paragraphs **70, 71, 82, 83 and 84** below;
- s. Ensuring that records are retained, and the HTA, third party procurement organisations, organisations responsible for human application, relevant third parties and other relevant tissue establishments are notified without delay of any serious adverse event and / or serious adverse reaction in accordance with paragraph **99** below. This is in addition to his / her duty to notify the HTA of serious adverse events and / or serious adverse reactions (including suspected serious adverse events and / or serious adverse reactions) and to provide the necessary report to the HTA in accordance with paragraph 4 (d) of Directions 001/2006 and paragraphs **100 and 101** below;
- t. Ensuring that third parties, with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph **117 (a)** below, notify the establishment and / or the HTA of the actions taken by the third party, with respect to other implicated tissues

and / or cells that have been distributed for human application in accordance with paragraph **99** below;

- u. Ensuring that where a third party carries out the activity of distribution on behalf of the LH, that the third party provides information to organisations responsible for human application of tissues and / or cells about how those organisations should report serious adverse reactions in accordance with paragraph **99** below;
- v. Ensuring, in conjunction with the LH, that any third party, with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph **117** below, establishes and maintains an accurate, rapid and verifiable recall procedure which complies with the provisions of these Directions, as amended from time to time in accordance with paragraph **107** below;
- w. Ensuring, in conjunction with the LH, that all imports of human tissues and / or cells from non EEA states meet standards of quality and safety equivalent to those set down in the Regulations, the Directives and as set out in Directions given by the HTA from time to time and in accordance with paragraph **111** below;
- x. Ensuring that any third party, with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph **117** below, is made aware of, and furnished with, copies of all regulatory alerts or other relevant communications from the HTA regarding serious adverse events and / or serious adverse reactions without delay;
- y. Ensuring that all personnel and third parties, with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph **117** below, are aware at all times that the requirements of any Directions given by the HTA from time to time including Directions 001/2006 and these Directions represent suitable practices in the course of the carrying on of the licensed activity or activities or activity or activities carried out under the third party agreement; and
- z. Ensuring that any third party, with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph **117** below, is provided with copies of any Directions given by the HTA from time to time, which are relevant to the activity or activities carried out under the third party agreement by the third party or relevant to the provision of goods or services under the

third party agreement, as soon as possible after issue of the Directions by the HTA. In particular the DI must ensure that copies of Directions 001/2006 and these Directions are furnished to any third party before any activity or activities are carried out by the third party on behalf of the LH.

13. The duty regarding the maintaining, making available and holding of information collected in pursuance of a licence or third party agreement in accordance with paragraph 12 (q) above will continue to apply following any substitution or retirement of the DI.

Requirements for Holding Licence

14. Paragraph 10 of Directions 001/2006 is hereby amended and replaced by this paragraph. The HTA is regulating establishments that store, procure, test, process, distribute, import or export tissues and / or cells intended for human application via the Regulations by: –
 - a. Requiring persons who store tissues and / or cells intended for human application to obtain and maintain a licence from the HTA;
 - b. Requiring persons carrying out the activities of procurement, testing, processing, distribution, import or export of tissues and / or cells intended for human application to carry out such activity or activities under the authority of a licence granted by the HTA under the Regulations or alternatively in pursuance of a third party agreement established in accordance with paragraph **117 (a)** below; and
 - c. Where the activities of procurement, testing, processing, distribution, import or export of tissues and / or cells intended for human application are carried out in pursuance of a third party agreement, requiring the LH and the DI to ensure that third party agreements are maintained in accordance with the requirements of the Regulations and these Directions and that appropriate SOPs are in place and complied with in accordance with the requirements of the Regulations, these Directions and Directions 001/2006.

Organisation and management

15. The establishment shall have an organisational structure and operational procedures appropriate to the activity or activities for which it is licensed. The organisational structure shall

ensure that all medical, scientific, nursing and other staff are sufficiently involved in order that the requirements of these Directions, Directions 001/2006 and the Directives are met and to secure the effective operation of the quality management system.

16. The establishment shall have an organisational chart which clearly defines accountability and reporting relationships within the establishment.
17. The establishment shall have access to a nominated registered medical practitioner and / or qualified scientific adviser, if appropriate, to provide advice on and to oversee the establishment's medical and scientific activities including the selection criteria for donors of tissues and / or cells as laid down in Annex A of Directions 001/2006, review of the outcomes of the laboratory tests which must be carried out in accordance with Annex B of Directions 001/2006, review of clinical outcomes of applied tissues and / or cells or interaction as appropriate with clinical users.
18. The establishment shall put in place and maintain a documented quality management system which is applied to the activity or activities for which it is licensed in accordance with the standards laid down in the Directives, Directions 001/2006 and these Directions, as amended from time to time.
19. The establishment's management including the DI and the LH shall be committed to the establishment, maintenance and continual improvement of the quality management system and shall in particular: –
 - a. Set, maintain and update quality objectives;
 - b. Appoint a quality manager who is suitably qualified and responsible for ensuring that the quality management system maintained by the establishment is implemented throughout the establishment and continually updated and improved in accordance with the principles of good practice, Directions 001/2006, these Directions and such other Directions as given by the HTA from time to time. The person appointed as quality manager in accordance with this sub paragraph may be an existing member of staff with other duties provided he / she can fulfil the duties of quality manager and is suitably qualified;
 - c. Establish a quality policy which incorporates the requirements of the Directives, Directions 001/2006 and these Directions, as amended from time to time, the

principles of good practice and the health, safety and welfare of personnel of, and visitors to, the establishment and intermediate and end users of the tissues and / or cells;

- d. Conduct regular management reviews of the establishment's quality management system and document the results of the review including all decisions and actions agreed and taken to improve the effectiveness of the quality management system and service provided by the establishment;
 - e. Make available the necessary resources in terms of facilities, personnel, equipment and materials and data and information systems to ensure the effective implementation and continual improvement of the establishment's quality management system; and
 - f. Ensure that the organisational chart including the responsibilities and reporting relationships are communicated to all personnel within the establishment and that all personnel are aware of the importance of ensuring that the quality management system maintained by the establishment is effective and continually improved as appropriate.
20. The establishment shall be an entity that can be held legally responsible for its activities.
21. The establishment must ensure that the risks inherent in the use and handling of biological material are identified and minimised, consistent with maintaining adequate quality and safety for the intended purpose of the tissues and / or cells. This includes risks relating in particular to the procedures, environment and staff health status specific to the establishment.
22. The establishment shall ensure that third party agreements comply with the requirements of the Regulations, Directions 001/2006 as amended by these Directions and these Directions in accordance with paragraphs **118** and **119** below. All third party agreements must specify the terms of the relationship and responsibilities of the parties involved together with the protocols to be followed by both parties to meet the required performance specifications.
23. The establishment shall ensure that there is a documented system in place, which is supervised by the DI, for ratifying that tissues and / or cells intended for human application meet

appropriate specifications for safety and quality for release and for their distribution.

24. In the event of the termination of activities for whatever reason (including closure of the establishment or third party establishment with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph **117(a)** below), the agreements concluded and / or the SOPs adopted in accordance with the parent directive shall include traceability data and material concerning the quality and safety of the tissues and / or cells. The requirement to have an SOP and / or agreement regarding the transfer of tissues and / or cells to another licensed establishment or establishments in the event of termination of activities is in accordance with paragraph 53 of Directions 001/2006 as extended by this paragraph and paragraph **123** below.
25. The establishment shall put in place and maintain a documented system that ensures the identification of every unit of tissue and / or cells at all stages of the activity or activities for which the establishment is licensed. This system shall include the SOP referred to in paragraph 54 of Directions 001/2006 and shall be in accordance with paragraphs **79–83**. Where an activity is or activities are carried out by a third party pursuant to a third party agreement established in accordance with paragraph **117(a)**, and paragraph **117 (b)** where appropriate, below, the LH shall secure that the third party complies with the requirements of this paragraph.

Personnel

26. The DI shall ensure that at all times there are sufficient numbers of qualified staff to ensure that the requirements of the Regulations and the Second Commission Directive are satisfied.
27. The establishment shall put in place and maintain an SOP for personnel management that ensures that all personnel have: –
 - a. Clear, documented and up-to-date job descriptions, that set out the tasks, responsibilities and accountabilities of each member of staff;
 - b. A full understanding of the tasks, responsibilities, and accountabilities assigned to them under their job description, and any amendments or modifications to such job descriptions during the course of their employment;

- c. Competence evaluation and assessment at regular intervals as laid down in the establishment's quality system;
 - d. Initial / basic training and updated training that ensures that personnel are competent to carry out their assigned tasks and responsibilities including training in the management of equipment and materials, as appropriate;
 - e. Updated training as required when procedures change or scientific knowledge develops;
 - f. Adequate opportunities for relevant and continuing education and professional development, which shall be documented and maintained by the establishment as part of their personnel records; and
 - g. Sufficient access to internal communications and relevant communications from the HTA as appropriate.
28. The establishment shall ensure that the training programme for personnel secures and documents that each individual: –
- a. Has competence in the performance of their designated tasks;
 - b. Has an adequate knowledge and understanding of the scientific / technical processes and principles relevant to their designated tasks;
 - c. Understands the organisational framework, quality system and health and safety rules of the establishment in which they work; and
 - d. Is adequately informed of the broader ethical, legal and regulatory context of their work.
29. The establishment shall ensure that a continuing education and professional development programme is available to all personnel at all levels and shall make available the necessary resources to ensure that all personnel have adequate opportunities to avail of such continuing education and professional development programmes.
30. The establishment shall maintain personnel records for all personnel that includes, as a minimum, the following information: –
- a. Terms and conditions of employment;

- b. Job description;
- c. Employment contract / letter of appointment;
- d. Relevant educational and professional qualifications;
- e. Record of induction and orientation;
- f. Record of health and safety training;
- g. Record of education and training, including updated training and continuing education and professional development programmes;
- h. Certificate(s) of registration with appropriate professional and / or statutory bodies;
- i. Occupational Health Record;
- j. Disciplinary Record; and
- k. Sickness and Absence Record.

The establishment shall maintain the confidentiality of personnel records in accordance with national legislation, guidelines and good practice.

- 31. The establishment shall ensure that personnel records are available for inspection by a duly authorised person or persons on behalf of the HTA, upon request.

Equipment and materials

- 32. The establishment shall ensure that it has the equipment and materials necessary for the effective carrying out of the activity or activities for which it is licensed, and which complies with the requirements of the Directives, and in particular, the Second Commission Directive.
- 33. The establishment shall put in place and maintain an SOP for the management of equipment and materials that ensures: –
 - a. That equipment and materials are selected and procured on the basis that they are designed and fit for their intended purpose and must minimise any hazard to recipients and / or personnel;
 - b. Instructions for use and maintenance, including steps to be taken in the event of any malfunction or failure, are

communicated to all personnel using the equipment and materials in the course of their employment;

- c. The identification, validation of all critical equipment and technical devices, including regular inspection;
- d. That all critical equipment and technical devices are preventively maintained in accordance with the manufacturer's instructions;
- e. Identification of equipment or materials that affect critical processing or storage parameters (example – temperature, pressure, particle counts, microbial contamination levels), and subjecting them to appropriate monitoring, alerts, alarms and corrective action, as required, to detect malfunctions and defects and to ensure that the critical parameters are maintained within acceptable limits at all times;
- f. Calibration of equipment with a critical measuring function against traceable standards where available;
- g. That new and repaired equipment is tested upon installation and validated prior to use;
- h. That test results and outcomes of inspections, testing and validations are documented and maintained;
- i. Maintenance, servicing, cleaning, disinfection and sanitation of all critical equipment is performed regularly, and is documented and maintained;
- j. That procedures for the operation of each piece of critical equipment, detailing the action to be taken in the event of a malfunction or failure, is available at all times and to all users;
- k. That the procedures for the activity or activities for which the establishment is licensed, detail the specifications for all critical materials and reagents, including in particular, defining specifications for additives (example solutions) and packaging materials;
- l. That critical reagents and materials meet documented requirements and specifications, and where applicable, the requirements of EC Directives 93/42/EC of 14 June 1993 concerning medical devices, and 98/79/EC of 27 October 1998 on in vitro diagnostic medical devices;

- m. The recording and reporting of any serious adverse event in accordance with paragraphs **100** and **101** below;
 - n. That inventory records are maintained, and controls carried out, as appropriate;
 - o. That all relevant personnel are trained in the management of equipment and materials, as appropriate; and
 - p. That all relevant data relating to products and material coming into contact with tissues and / or cells is traceable in accordance with the requirements of the Directives, Directions 001 / 2006 and these Directions, as amended from time to time.
34. The establishment shall retain documented records evidencing compliance with the SOP referred to in paragraph 33 above and the procedures and requirements for the management of equipment and materials.

Facilities and premises

35. The establishment shall have facilities and premises suitable for the carrying out of the activity or activities for which it is licensed, including, as appropriate, clinical facilities, laboratory facilities, storage facilities, facilities for reception and procurement, facilities for distribution, import and / or export, where relevant facilities for donation, and facilities for staff.
36. The establishment shall put in place and maintain an SOP for the maintenance of its premises and facilities, which includes as a minimum: –
- a. Controlled access to premises and facilities, as appropriate;
 - b. Health, safety and welfare of all staff;
 - c. Action to be taken in the event of an emergency;
 - d. Cleaning and maintenance of all facilities;
 - e. Regular audit of facilities;
 - f. Disposal of waste, including clinical waste; and
 - g. Re-provision of services following an emergency.

37. The establishment shall ensure that all clinical facilities available, at all times: –
- a. Are suitable and appropriate for the activity or activities for which the establishment is licensed;
 - b. Have appropriate back-up and emergency clinical facilities which are appropriate to the degree of risk involved in the activity or activities and which accord with the standard practice in medical provision;
 - c. Where the licensed activity of processing is included on the establishment's licence, provide for the processing to take place in an environment with specified air quality and cleanliness in accordance with paragraphs **39** to **42** below;
 - d. Provide for the health, safety and privacy of living donors and respect and dignity of deceased donors.
38. The establishment shall ensure that its laboratory facilities, at all times: –
- a. Provide a safe working environment for all staff in accordance with national legislation and guidelines;
 - b. Where the licensed activity of processing is included on the establishment's licence, provide for the processing to take place in an environment with a specified air quality and cleanliness in accordance with paragraphs **39** to **42** below;
 - c. Are fit for purpose and appropriate for the activity or activities for which the establishment is licensed.
39. Where the activity of processing of tissues and / or cells is included on the establishment's licence, the establishment shall ensure that this takes place in an environment with specified air quality and cleanliness to minimise the risk of contamination, including cross contamination between donations, and to protect their quality and safety at all times. The establishment shall validate and monitor the effectiveness of these measures at appropriate intervals.
40. Unless otherwise specified in paragraph **41** below, where tissues or cells are exposed to the environment during processing, without a subsequent microbial inactivation process, an air quality with 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 and EU Directive 2003/94/EC is required with a background environment appropriate for the processing of the tissue or cell concerned, but at least equivalent to GMP Grade D in terms of particles and microbial counts.

41. A less stringent environment than specified in paragraph **40** above may be acceptable where: –
 - a. A validated microbial inactivation or validated terminal sterilisation process is applied;
 - b. Or, 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;
 - c. Or, 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 tissue and / or cell transplantation; and
 - d. Or, where it is not technically possible to carry out the required process in a Grade A environment (for example, due to the requirements for specific equipment in the processing area that is not fully compatible with a Grade A environment).
42. Where the establishment seeks to rely on one or more of the alternatives mentioned in paragraph **41** above, an environment must be specified. The establishment shall demonstrate and document that the chosen environment achieves the quality and safety required, at least taking into account the intended purpose, the mode of application and the immune status of the recipient. The establishment shall ensure that appropriate garments and equipment are provided in every relevant department of the establishment to secure personal protection and hygiene and that written hygiene and gowning instructions are available in each department of the establishment, as appropriate.
43. Where the activity of storage is included on the establishment's licence, the establishment shall ensure that the storage facilities for tissues and / or cells: –
 - a. Are fit for purpose and appropriate;
 - b. Provide for the storage of tissues and / or cells in conditions that ensure their quality and safety at all times;

- c. Provide for the storage conditions necessary to maintain the required tissue and cell properties to be defined, to include relevant parameters such as temperature, humidity or air quality;
 - d. Provide for critical parameters such as temperature, humidity or air quality to be controlled, monitored and recorded in order to demonstrate compliance with the specified storage conditions;
 - e. Provide for emergency and back-up procedures to deal with any failure of storage conditions and / or damage or destruction of storage vessels;
 - f. Provide for the separation of tissues and / or cells prior to release and those in quarantine from those that are released and from those that are rejected, in order to prevent cross-contamination and mix-up;
 - g. Provide physically separate areas or storage devices or secured segregation within the storage device in both quarantine and released storage locations for holding certain tissues and / or cells collected in compliance with special criteria;
 - h. Be designed to avoid and minimise contact with chemical or atmospheric contamination and any known potential sources of infection; and
 - i. Provide for controlled access and all appropriate security measures to prevent access by non authorised personnel.
44. The establishment shall have and maintain appropriate staff facilities at all times and shall ensure that staff are provided with appropriate garments and equipment for personal protection and hygiene, together with instructions for their use.

Documentation and records

- 45. The establishment shall put in place and maintain a system that results in clearly defined and effective documentation, correct records and registers, and authorised SOPs for the activity or activities for which the establishment is licensed.
- 46. The system established and maintained in accordance with paragraph **45** above shall include, as a minimum, arrangements for: –

- a. Reviewing documents and records regularly to ensure conformity with the requirements of Directions 001/2006, these Directions, as amended from time to time, the Directives, the Regulations and any supplemental Directions given by the HTA to ensure compliance with the Regulations;
- b. Ensuring that work performed is standardised and that all steps are traceable, such as coding, donor eligibility, procurement, processing, storage, transportation, distribution, import and export and disposal, including aspects relating to quality control and quality assurance;
- c. Identifying and documenting the materials, equipment and personnel involved for every critical activity;
- d. Reviewing, dating, approving and documenting all changes to documents within the establishment, and ensuring that changes to documents are implemented promptly by authorised personnel;
- e. Establishing and maintaining a document control procedure to provide for the history of document reviews and changes and to ensure that only current versions of documents are in use;
- f. Establishing and maintaining procedures to ensure that records are shown to be reliable and a true representation of the results;
- g. Establishing and maintaining procedures to ensure that records are legible and indelible and whilst they may be handwritten, the procedures must protect the records when they are transferred to another validated system, such as a computer or microfilm;
- h. Establishing and maintaining procedures for the maintenance of all records including raw data, which are critical to the safety and quality of tissues and / or cells. Without prejudice to Article 9 (2) of the Second Commission Directive, all records, including raw data, which are critical to the safety and quality of tissues and / or cells shall be kept so as to ensure access to this data for at least 10 years after expiry date, clinical use or disposal (or such longer period as may be specified by the HTA in Directions);
- i. Preventing unauthorised disclosure of information and records and ensuring that records meet the confidentiality

requirements of the Regulations, Directions 001/2006 and these Directions, as amended from time to time;

- j. Ensuring that access to registers and data is restricted to persons authorised by the DI and to the HTA for the purpose of inspection and control measures; and
- k. Establishing and maintaining procedures for the storage, archiving, retrieval and safe disposal of documentation and records that includes provision for disaster recovery.

Quality review

- 47. The establishment shall put in place and maintain an audit system for the activity or activities for which it is licensed. As a minimum, the audit system must ensure: –
 - a. That trained and competent personnel conduct the audit in an independent way at least every two years to verify compliance with approved protocols, regulatory requirements and the requirements of Directions 001/2006 and these Directions, as amended from time to time;
 - b. That findings and corrective actions are documented;
 - c. That any deviation from the required standards of quality and safety lead to a documented investigation, including a decision on possible corrective and preventive actions;
 - d. That the fate of non-conforming tissues and / or cells is decided in accordance with SOPs supervised by the DI and recorded;
 - e. That all affected tissues and / or cells are identified and accounted for;
 - f. That corrective actions are documented, initiated and completed in a timely and effective manner;
 - g. That preventive and corrective actions are assessed for effectiveness after implementation;
 - h. That processes are put in place and maintained for review of the performance of the quality management system to ensure continuous and systematic improvement; and
 - i. That the establishment completes a self assessment form assessing the establishment against the HTA's standards

every 6–12 months or within such earlier time as the HTA may require and in particular prior to an inspection of the establishment by the HTA. The establishment shall complete the first self-assessment form by the 1 September 2007 and all self-assessment forms must be retained, furnished to the HTA on request and made available to a duly authorised person or persons from the HTA at any inspection of the premises.

48. The quality review carried out in accordance with paragraph **47 (h)** above shall include, but not be limited to, consideration of the results of the identification, investigation, control, recording and notification of serious adverse events and / or serious adverse reactions. The results of the quality review shall be recorded and maintained, including all decisions and proposed actions related to the improvement of the quality management system.

Requirements for Holding Licence II – authorisation of tissue and cell preparation processes.

49. The establishment shall put in place and maintain a procedure for the receipt of tissues and / or cells from another establishment that complies with the First Commission Directive and Directions 001/2006 at paragraphs 43 to 47.
50. Where the activity of processing is included on the establishment's licence, the establishment's procedures must comply with the requirements of Directions 001/2006 and in addition, must comply, as a minimum, with the following criteria: –
 - a. The critical processing procedures must be validated and must not render the tissues and / or cells clinically ineffective or harmful to the recipient. This validation may be based on studies performed by the establishment, or on data from published studies or, for well established processing procedures, by retrospective evaluation of the clinical results for tissues and / or cells supplied by the establishment;
 - b. It has to be demonstrated that the validated process can be carried out consistently and effectively in the establishment's environment by the establishment's personnel;
 - c. The procedures must be documented in SOPs which must conform to the validated method and to the standards laid down in the Second Commission Directive

and these Directions and in particular paragraphs 45 to 46 above;

- d. It must be ensured that all processes are conducted in accordance with the establishment's approved SOPs;
 - e. Where a microbial inactivation procedure is applied to the tissues and / or cells, it must be specified, documented, and validated;
 - f. Before implementing any significant change in processing, the modified process must be validated and documented;
 - g. The processing procedures must undergo regular critical evaluation to ensure that they continue to achieve the intended results;
 - h. Procedures for discarding tissues and / or cells must prevent the contamination of other donations and products, the processing environment or personnel. These procedures must comply with national regulations and guidelines; and
 - i. It must be ensured that paragraphs 48 to 52 of Directions 001/2006 are complied with at all times.
51. Where the storage of tissues and / or cells is included on the establishment's licence, the establishment's procedures must comply, with the requirements of Directions 001/2006 and in addition, must comply, as a minimum, with the following criteria: –
- a. The maximum storage time must be specified for each type of storage condition. The selected period must reflect, among others, possible deterioration of the required tissue and / or cell properties;
 - b. There must be a system of inventory hold for tissues and / or cells to ensure that they cannot be released until all requirements laid down in the Directives, Directions 001/2006 and these Directions, as amended from time to time, have been satisfied. There must be a SOP that details the circumstances, responsibilities and procedures for the release of tissues and / or cells for distribution;
 - c. A system for the identification of tissues and / or cells throughout any phase of processing in the establishment must clearly distinguish released from non-released (quarantined) and discarded products;

- d. Records must demonstrate that before tissues and / or 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, within the establishment, was responsible for their release; and
 - e. A documented risk assessment approved by the DI must be undertaken to determine the fate of all stored tissues and / or cells following the introduction of any new donor selection or testing criterion or any significantly modified processing step that enhances safety or quality.
52. Where the activity of distribution is included on the establishment's licence, the establishment's procedures must comply with the requirements of Directions 001/2006 (subject to paragraph 5 (m) above) and in addition, must comply, as a minimum, with the following criteria: –
- a. Critical transport conditions, such as temperature and time limit must be defined to maintain the required tissue and / or cell properties;
 - b. The container/package must be secure and ensure that the tissues and / or cells are maintained in the specified conditions. All containers and packages need to be validated as fit for purpose;
 - c. Where distribution is carried out by a third party, the third party agreement established in accordance with paragraph **117 (a)** below must ensure that the required conditions are maintained at all times;
 - d. There must be personnel authorised within the establishment to assess the need for recall and to initiate and coordinate the necessary actions;
 - e. An effective recall procedure must be in place, including a description of the responsibilities and actions to be taken and notification to the HTA;
 - f. Actions must be taken within pre-defined periods of time and must include tracing all relevant tissues and / or cells and, where applicable, must include trace-back. The purpose of the investigation is to identify any donor who might have contributed to causing the reaction in the

recipient and to retrieve available tissues and / or cells from that donor, as well as to notify consignees and recipients of tissues and / or cells procured from the same donor in the event that they might have been put at risk;

- g. Procedures must be in place for the handling of requests for tissues and / or cells. The rules for allocation of tissues and / or cells to certain patients or health care institutions must be documented and made available to these parties upon request; and
 - h. A documented system must be in place for the handling of returned products including criteria for their acceptance into the inventory, if applicable.
53. Where the activity of distribution is included on the establishment's licence, the establishment must comply with the packaging and labelling requirements of Directions 001/2006 (subject to paragraph 5 (m) above) and the requirements for final labelling and external labelling as set out in paragraphs **54** and **55** below.
54. The establishment shall comply with the following requirements for final labelling for distribution: –
- a. The primary tissue / cell container must provide:
 - i. type of tissues and / or cells, identification number or code of the tissue / cells, and lot or batch number where applicable;
 - ii. identification of the establishment from which the tissues and / or cells have come;
 - iii. expiry date;
 - iv. in the case of autologous donation, this has to be specified (for autologous use only) and the donor / recipient has to be identified;
 - v. in the case of directed donations, the label must identify the intended recipient;
 - vi. when tissues and / or cells are known to be positive for a relevant infectious disease marker, it must be marked as: BIOLOGICAL HAZARD.

If any of the information under points (iv) and (v) 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;

- b. The following information must be provided either on the label or in accompanying documentation: –
 - i. description (definition) and, if relevant, dimensions of the tissue and / or cell product;
 - ii. morphology and functional data where relevant;
 - iii. date of distribution of the tissues and / or cells;
 - iv. biological determinations carried out on the donor and results;
 - v. storage recommendations;
 - vi. instructions for opening the container, package, and any required manipulation / reconstitution;
 - vii. expiry dates after opening / manipulation;
 - viii. instructions for reporting serious adverse events and / or serious adverse reactions as set out in paragraphs **100** and **101** below; and
 - ix. presence of potential harmful residues (e.g. antibiotics, ethylene oxide etc).
55. The establishment shall ensure that for transport, the primary container is placed in a shipping container that must be labelled with at least the following information: –
- a. Identification of the originating establishment, including an address and phone number;
 - b. Identification of the organisation responsible for human application of destination, including address and phone number;
 - c. A statement that the package contains human tissues and / 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.); and
 - f. Safety instructions / method of cooling (when applicable).
56. Where storage is the activity for which the establishment is licensed, the activities of procurement, testing, processing, distribution, import or export of tissues and / or cells intended for human application must be the subject of a third party agreement in accordance with paragraph **117 (a)** below. Alternatively, the establishment may apply to the HTA for a separate licence to carry out any of the activities of procurement, testing, processing, distribution, import and / or export of tissues and / or cells intended for human application.

Quality management

57. The establishment shall appoint a quality manager with specific responsibility for ensuring that the quality management system established in accordance with Directions 001/2006 is implemented and maintained. The quality manager should report to the establishment's management on the functioning and effectiveness of the quality management system and ensure that all personnel are aware of and comply with the establishment's quality management system at all times.
58. The quality manager should also have responsibility for ensuring that the audit and quality review required under paragraph **47** above is carried out including follow-up on all decisions and corrective and preventive actions taken or proposed following the audit and / or quality review.

Data Protection, confidentiality and disclosure

59. The establishment shall comply with the provisions regarding data protection and confidentiality contained in Directions 001/2006. The establishment shall also comply with the requirements of the Regulations on maintaining confidentiality and ensuring that information is not disclosed other than as permitted under the Regulations.
60. It shall be the duty of the DI, whether current or former and any third party, whether current or former, with whom the LH, or the DI on behalf of the LH, has a third party agreement, in accordance with paragraph **117** below, to ensure that all information which is collected in pursuance of a licence or a third party agreement, established in accordance with paragraph **117** below, or Directions 001/2006, or these Directions, as amended from time to time: –

- a. Is available for the purpose of tracing donations;
 - b. Is kept up-to-date and corrected without delay, where any discrepancy relating to such information is identified, whether by the HTA or otherwise; and
 - c. Is held securely and is subject to safeguards against unauthorised additions, deletions, modifications or transfer of information.
61. The SOP established and maintained in accordance with Directions 001/2006 for the control of access to health data and records must: –
- a. Include the necessary arrangements put in place and maintained by the DI in accordance with paragraph **60** above.
 - b. Designate an identified individual within the establishment with responsibility for monitoring, receiving, checking and arranging authorised access to confidential data and records in accordance with paragraph **63** below; and
 - c. Be reviewed regularly and updated as necessary in accordance with any additional Directions given by the HTA.
62. Any third party agreement established and maintained in accordance with paragraph **117** below shall include as a duty of the third party, whether current or former, the duty set out in paragraph **60** above.
63. The establishment and, in particular, the LH and any third party, shall ensure that any information which is collected in pursuance of a licence or a third party agreement established and maintained in accordance with paragraph **117** below, and from which a donor, whether living or deceased, or recipient of tissues and / or cells may be identified, is not disclosed, except where such disclosure is permitted under the terms of the Regulations. The HTA will issue separate guidance to LHs and DIs on the Information and Disclosure provisions of the Regulations.
64. Any agreement in relation to the termination of the licensed activity or activities at the establishment, or termination of the activity or activities of any third party (including closure of the establishment or third party establishment), entered into in accordance with paragraph **123** below must make provision for, and include the duty of former DIs and former third parties referred to in paragraphs **60** and **62** above.

65. Where the establishment or a third party, with whom the LH, or the DI on behalf of the LH, has a third party agreement, makes an authorised disclosure pursuant to any consent to disclosure given by the donor or recipient of the tissues and / or cells, whose identity would be disclosed, such consent to disclosure must be in a format approved by the HTA.

Procurement and distribution

66. No person shall procure tissues and / or cells for human application except in accordance with Directions given by the HTA including Directions 001/2006, these Directions and any supplementary or amending Directions.
67. The LH shall secure: –
- a. That procurement organisations comply with the requirements of paragraph 14 of Directions 001/2006; and
 - b. That procurements organisations and organisations responsible for human application of tissues and / or cells comply with the requirements for notification of serious adverse events and serious adverse reactions, in accordance with paragraph **98** below;
 - c. That the establishment complies with the requirements for retention of records, notification of any serious adverse event or events that occur during procurement and the provision of information to organisations responsible for human application of tissues and / or cells about how those organisations should report serious adverse events and / or serious adverse reactions in accordance with paragraph **98** below; and

and the DI shall secure: –

- d. That procurement organisations, organisations responsible for human application of tissues and / or cells and third parties, with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph 117 (a) below, retain the records referred to in paragraph **99** below and that the establishment, the HTA and other relevant tissue establishments are notified without delay of any serious adverse event which may influence the quality or safety of tissues and / or cells, or any serious adverse reaction which may influence or be linked to the quality or safety of tissues and / or cells;

- e. That, where a third party carries out the activity of distribution on behalf of the LH, the third party provides information to organisations responsible for human application of tissues and / or cells about how those organisations should report serious adverse reactions in accordance with paragraph **99 (b)** below; and
 - f. That, third parties, with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph 117 (a) below, comply with the notification requirements of the actions taken by third parties, with respect to other implicated tissues and / or cells that have been distributed for human application in accordance with paragraph **99 (d)** below.
68. Where procurement is an activity included on the establishment's licence, the LH shall secure compliance with the requirements of paragraphs 25 to 32 and 43 to 47 inclusive of Directions 001/2006.
69. A LH authorised to procure tissues and / or cells for human application or third parties responsible for procurement under a third party agreement may not distribute specified tissues and / or cells directly from where procurement takes place to an organisation responsible for human application for immediate human application unless the prior approval of the HTA has been obtained in accordance with paragraph **110** below. Where approval is given by the HTA, the LH and / or third party must nonetheless comply with the requirements of paragraph **52** above as appropriate.

Donor documentation and records

70. The establishment shall collect and retain, as a minimum, the following data for a period of at least thirty years (or such longer period as may be specified by the HTA in Directions) in an appropriate and readable storage medium: –
- a. Donor identification – donor identification that will include at least: –
 - i. Identification of the procurement organisation or establishment;
 - ii. Unique donation identification number;
 - iii. Date of procurement;
 - iv. Place of procurement;

- v. Type of donation (for example single or multi-tissue, autologous or allogeneic, living or deceased).
- b. Product identification that will include at least: –
- i. Identification of the establishment;
 - ii. Type of tissue and / or cell / product (basic nomenclature);
 - iii. Pool number (if applicable);
 - iv. Split number (if applicable);
 - v. Expiry date;
 - vi. Tissue and / or cell status (i.e. quarantined, suitable for use etc);
 - vii. Description and origin of the product or products, processing steps applied, materials and additives coming into contact with the tissues and / or cells and having an effect on their quality and / or safety; and
 - viii. Identification of the facility / establishment issuing the final label.
- c. Human application identification that will include at least: –
- i. Date of distribution and / or disposal; and
 - ii. Identification of the clinician or end user / facility / establishment.
71. The DI, in conjunction with the LH, shall secure that organisations responsible for human application retain the following data for a period of at least thirty years (or such longer period as may be specified by the HTA in Directions), in an appropriate and readable storage medium: –
- a. Identification of the supplier establishment;
 - b. Identification of the clinician or end user / facility / establishment;
 - c. Type of tissues and / or cells;

- d. Product identification;
 - e. Identification of the recipient; and
 - f. Date of application.
72. The establishment shall retain the information contained in the European coding system in accordance with paragraph **83** below. The HTA will issue further guidance and / or Directions when the detailed requirements of the European Coding System required by the parent directive are clarified by the European Commission. The DI, in conjunction with the LH, shall ensure that third parties responsible for human application also retain the information contained in the European coding system set out in paragraph **83** below, or as specified from time to time by the HTA in guidance and / or supplemental Directions.
73. The establishment shall ensure that it retains the documentation and records required to secure compliance with paragraphs **45** and **46** above.

Tissue and cell processing and storage

74. The establishment shall comply with the requirements of tissue and / or cell processing and storage laid down in Directions 001/2006 as amended by these Directions.
75. The establishment shall not distribute any processed tissues and / or cells until satisfied that the requirements of Directions 001/2006, these Directions, as amended from time to time, and the Directives have been met.
76. The establishment shall ensure that the equipment used, the working environment and the process design, validation and control conditions are in compliance with the requirements of the Second Commission Directive and as set out in paragraph **50** above, including any modifications to the processes used in the preparation of tissues and / or cells.
77. Where the activity of processing is carried out by a third party on behalf of the LH, the LH, or the DI on behalf of the LH, and the third party must have a third party agreement in accordance with paragraph **117 (a)** below. The third party agreement must include provision for the transfer of tissues and / or cells to a licensed establishment or establishments (subject to the consent of the donor) in the event of the termination of activities by the third party, for whatever reason (including closure of the third party establishment).

78. The establishment shall comply with the requirements of paragraphs **50** and **51** above in relation to processing and storage. Where processing is carried out by a third party pursuant to a third party agreement, the DI shall secure that the third party complies with paragraphs **50** and **51** above.

Traceability and coding

79. The establishment shall ensure that all tissues and / or cells donated, procured, tested, processed, stored, distributed and imported or exported are traceable from donor to recipient and vice versa at all times. The establishment shall maintain the SOP referred to in paragraph 54 of Directions 001/2006 which shall include tissues and / or cells donated, tested and imported or exported by or on behalf of the establishment.
80. The establishment shall have effective and accurate systems to uniquely identify and label all tissues and / or cells received and distributed in order to comply with the provisions of the Second Commission Directive. Where an activity is or activities are carried out by a third party pursuant to a third party agreement established in accordance with paragraph **117 (a)** below, the LH shall secure that the third party complies with the requirements of this paragraph.
81. The establishment shall retain, and the DI, in conjunction with the LH shall ensure that organisations responsible for human application retain, the minimum information set out at paragraphs **70** and **71** above for a period of at least thirty years (or such longer period as may be specified by the HTA in Directions), in an appropriate and readable storage medium.
82. The establishment shall ensure that a single European identifying code is allocated to all donated material at the establishment to ensure: –
- a. Proper identification of the donor;
 - b. Traceability of all donated material; and
 - c. Provision of information on the main characteristics and properties of tissues and / or cells.
83. The establishment shall ensure that the code referred to in paragraph **82** above shall incorporate, as a minimum the following information: –
- a. Donation identification:
 - i. Unique ID number; and

- ii. Identification of the establishment; and
- b. Product identification:
 - i. Product Code (basic nomenclature);
 - ii. Split number (if applicable); and
 - iii. Expiry date.

The HTA will issue further guidance and / or Directions when the detailed requirements of the European Coding System required by the parent directive are clarified by the European Commission.

- 84. The DI, in conjunction with the LH, shall ensure that third parties carrying out activities on behalf of the LH pursuant to a third party agreement in accordance with paragraph **117 (a)** below retain the minimum information referred to in paragraph **83** above.
- 85. The establishment shall ensure that any agreement in relation to the termination of licensed activities, established in accordance with paragraph **123** below, whether by the establishment itself or by any third party with whom the LH, or DI on behalf of the LH, has a third party agreement in accordance with paragraph **117 (a)** below, includes provision for the transfer of the minimum information referred to in paragraphs **70, 71, 82** and **83** above to another licensed establishment or establishments.
- 86. The DI and any third party, with whom the LH, or the DI on behalf of the LH, has a third party agreement established in accordance with paragraph **117 (a)** below, shall ensure that the minimum information referred to in paragraphs **70, 71, 82** and **83** above is available for the purpose of tracing donations.
- 87. Any information which is collected under a licence or third party agreement, established in accordance with paragraph **117** below and from which a donor, whether living or deceased, or recipient of tissues and / or cells may be identified, may be disclosed to the establishment for the purpose of tracing donations.

Register and reporting

- 88. The registers established and maintained by the establishment in accordance with paragraph 57 of Directions 001/2006 shall also include the following: –

- a. A record of the types and quantities of tissues and / or cells imported and / or exported and on the origin and destination of such imported and / or exported tissues and / or cells intended for human application;
 - b. A record of whether the tissues and / or cells are autologous or allogenic; and
 - c. The coded data assigned to each donor and donation of tissues and / or cells in accordance with paragraph 54 of Directions 001/2006 and paragraphs **82** to **83** above.
89. The LH and / or DI shall ensure that third parties with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph **117 (a)** below, maintain the registers referred to in paragraph 57 of Directions 001/2006 as supplemented by paragraph **88** above.
90. The establishment, and any third party with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph **117 (a)** below, shall retain the registers and information referred to in paragraph 57 of Directions 001/2006 and paragraph **88** above: –
- a. for a minimum of 30 years or such longer period as may be specified by the HTA in Directions; and
 - b. in a format which ensures that the information retained can easily be extracted and submitted electronically to the HTA on an annual basis in accordance with paragraph **93** below.
91. The establishment, and any third party with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph **117 (a)** below, shall ensure that such registers and information as referred to in paragraph **90** above are available for inspection at all times by a duly authorised person or persons on behalf of the HTA.
92. The Annual Report, which the establishment must submit to the HTA in accordance with paragraph 58 of Directions 001/2006, shall include: –
- a. the additional information referred to in paragraph **88** above; and
 - b. a report of the activities of any third parties with whom the LH, or the DI on behalf of the LH, has a third party

agreement in accordance with paragraph **117 (a)** below.

93. The Annual Report, which the establishment must submit to the HTA in accordance with paragraph 58 of Directions 001/2006, shall be submitted to the HTA by the 31 January each year covering the previous calendar year's activities. This Report shall be in a format acceptable to the HTA as may be specified from time to time.
94. The HTA shall maintain a register recording: –
- a. The grant, suspension or revocation of every licence granted under the Regulations;
 - b. The name of the LH;
 - c. The activity or activities for which the establishment has been licensed; and
 - d. Any variation in LH and / or the activity or activities for which the establishment is licensed.

The HTA shall make such of the information contained in the above register available to the public, as it considers appropriate.

95. The HTA shall maintain a register of information regarding serious adverse events and serious adverse reactions in accordance with paragraph **105** below. The HTA shall make such of the information contained in this register available to the public, as it considers appropriate.
96. In the event of the termination of activities, for whatever reason (including closure of the establishment or the third party establishment), the establishment, and any third party with whom the LH, or the DI on behalf of the LH, has a third party agreement, established in accordance with paragraph **117 (a)** below, must ensure that the registers, documentation, records and information retained pursuant to Directions 001/2006 and these Directions, as amended from time to time, are transferred to another licensed establishment or establishments.

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

97. Paragraph 60 (f) and (g) of Directions 001/2006 shall apply to tissues and / or cells exported by the establishment or by a third party on behalf of the LH pursuant to a third party agreement, established in accordance with paragraph **117 (a)**

below. Paragraph 60 (i) of Directions 001/2006 shall be read as including reference to establishments engaged in importing and / or exporting tissues and / or cells.

98. The LH shall ensure that: –
- a. Procurement organisations with whom the LH, or the DI on behalf of the LH, has a third party agreement have the necessary procedures in place to retain the records of tissues and / or cells procured and to notify the establishment and other relevant tissue establishments, as appropriate, without delay of: –
 - i. Any serious adverse event or events that occur during procurement which may influence the quality and / or safety of tissues and / or cells; and
 - ii. Any serious adverse reaction or reactions in the living donor which may influence the quality and / or safety of tissues and / or cells;
 - b. Organisations responsible for human application of tissues and / or cells have procedures in place to retain the records of tissues and / or cells applied and to notify the establishment, and other relevant tissue establishments, as appropriate, without delay of: –
 - i. Any serious adverse event or events that may influence the quality and / or safety of tissues and / or cells; and
 - ii. Any serious adverse reaction or reactions observed during and after clinical application which may be linked to the quality and / or safety of tissues and / or cells;
 - c. The establishment has the necessary procedures in place to retain the records of tissues and / or cells procured and to notify other relevant tissue establishments, as appropriate, without delay of any serious adverse event or events that occur during procurement which may influence the quality and / or safety of tissues and / or cells;
 - d. Where the establishment is licensed to distribute tissues and / or cells for human application, the establishment provides information to any organisation responsible for human application of tissues and / or cells about how that organisation should report serious adverse reactions as

specified in sub-paragraph (b) above; and

- e. The establishment provides information to organisations responsible for human application of tissues and / or cells about how those organisations should report serious adverse events as specified in sub-paragraph (b) above.
99. The DI shall ensure that: –
- a. Procurement organisations with whom the LH, or the DI on behalf of the LH, has a third party agreement and organisations responsible for human application of tissues and / or cells retain the records and notify the establishment, other relevant tissue establishments, as appropriate, and the HTA without delay of any serious adverse event or serious adverse reaction as referred to in paragraph **98** above;
 - b. Where a third party carries out the activity of distribution on behalf of the LH, that the third party provides information to any organisation responsible for human application of tissues and / or cells about how that organisation should report serious adverse reactions as specified in paragraph **98 (b)** above;
 - c. Third parties, with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph **117 (a)** below, retain the records and notify the establishment, other relevant tissue establishments, as appropriate, and the HTA without delay of any serious adverse event or serious adverse reaction as referred to in paragraph **98** above; and
 - d. Third parties, with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph **117 (a)** below, notify the establishment and / or the HTA of the actions taken by the third party, with respect to other implicated tissues and / or cells that have been distributed for human application.
100. The SOP established and maintained in accordance with paragraph 60 of Directions 001/2006 shall secure: –
- a. The inclusion of procedures to retain the records and to notify other tissue establishments, as appropriate, without delay of any serious adverse event that occurs during procurement which may influence the quality and / or safety of tissues and / or cells;

- b. The inclusion of procedures to retain the records and to notify other tissue establishments, as appropriate, without delay of any serious adverse reaction, which may influence the quality and / or safety of tissues and / or cells;
- c. The communication and notification by the DI without delay of all relevant available information about suspected serious adverse events and / or serious adverse reactions notified to it by procurement organisations, organisations responsible for human application and / or third parties, with whom the LH, or DI on behalf of the LH has a third party agreement in accordance with paragraph **117 (a)** below, or of which it becomes aware;
- d. The provision by the DI to the HTA without delay of the conclusion of the investigation to analyse the cause and the ensuing outcome of any serious adverse event and / or serious adverse reaction;
- e. Notification by the DI to the HTA of the information contained in and set out in Parts A of Annexes A and B to these Directions. Such notification shall be in a format approved by the HTA. The HTA's approved notification system is available online on the HTA's website and should be used at all times;
- f. The evaluation of serious adverse events by the establishment to identify preventable causes within the process;
- g. Notification to the HTA of the actions taken, by the establishment or third parties, with whom the LH, or DI on behalf of the LH, has a third party agreement in accordance with paragraph 117 (a) below, with respect to other implicated tissues and / or cells that have been distributed for human application;
- h. Notification by the DI to the HTA of the conclusion of the investigation in the form and containing, at least, the information contained in Parts B of Annexes A and B to these Directions. Such notification shall be in a format approved by the HTA. The HTA's approved notification system is available online on the HTA's website and should be used at all times; and
- i. The inclusion of procedures to notify, and provide to, any third party, with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with

paragraph **117 (a)** below, and paragraph **117 (b)** below, where appropriate, copies of all regulatory alerts or other relevant communications from the HTA regarding serious adverse events and / or serious adverse reactions without delay in accordance with paragraph **12 (x)** above.

101. The DI must notify the HTA of any suspected serious adverse event and / or suspected serious adverse reaction as soon as possible after the incident or after notification by procurement organisations, organisations responsible for human application of tissues and / or cells and / or third parties. The DI must provide to the HTA, at least the information contained in Parts A and B of Annexes A and B to these Directions. Such notification shall be in a format approved by the HTA. The HTA's approved notification system is available online on the HTA's website and should be used at all times.
102. Following notification of any suspected serious adverse event or suspected serious adverse reaction, the HTA shall investigate and carry out such control measures that are deemed appropriate in all the circumstances.
103. The investigation and control measures referred to in paragraph **102** above may include but not be limited to: –
 - a. Inspection of the establishment, relevant third party premises and the facilities of any third party with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph **117** below including inspections carried out on behalf of the competent authorities of other EEA member states;
 - b. Evaluation and verification of procedures and activities carried out at the establishment and / or the facilities of third parties or relevant third party premises with whom the LH, or the DI on behalf of the LH, has a third party agreement;
 - c. Examination of documents and records retained to ensure compliance with the Directives, the Regulations, Directions 001/2006 and these Directions, as amended from time to time; and
 - d. Communication of all necessary information to persons carrying out licensed activities, third parties carrying out activities on behalf of LHs, users of tissues and / or cells intended for human application, competent authorities in EEA member states and the European Commission as considered appropriate by the HTA to enable all appropriate action to be taken including withdrawal of

tissues and / or cells that are known or suspected to be unsuitable for human application.

104. The LH and / or DI shall ensure that any third party agreement entered into includes an obligation on the part of the third party to enable a duly authorised person or persons on behalf of the HTA to carry out the necessary investigation and control measures referred to in paragraphs **102** and **103** above. The HTA's statutory powers, including its powers to enter, inspect and search relevant third party premises and to observe the carrying-on of activities carried out under the third party agreement at relevant third party premises, are set out in the Regulations.
105. The HTA shall maintain a register in accordance with paragraph **95** above of serious adverse events and serious adverse reactions notified to it that includes: –
 - a. Any serious adverse event and / or serious adverse reaction attributable to the procurement, testing, processing, storage, distribution, or import or export of tissues and / or cells;
 - b. Any serious adverse event or serious adverse reaction which may influence the quality or safety of tissues and / or cells; and
 - c. Any serious adverse reaction which is observed during or after clinical application and which may be linked to the quality or safety of tissues and / or cells.
106. The establishment shall ensure that the recall procedure established and maintained in accordance with paragraph **52** above is documented, accurate and allows for the rapid and verifiable recall from distribution of any tissues and / or cells which may be related to any serious adverse event and / or serious adverse reaction.
107. The LH and / or DI shall ensure that any third party, with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph **117** below, imposes an obligation on the third party to establish and maintain an accurate, rapid and verifiable recall procedure which complies with the provisions of these Directions, as amended from time to time.

Import, export and distribution

108. Paragraph 64 (a) and (c) of Directions 001/2006 is hereby amended as follows. Establishments that import human

tissues and / or cells from states who are not members of the EEA shall take all necessary measures to ensure: –

- a. That such imports are undertaken by establishments licensed for that purpose, or by third parties with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph **117 (a)** below; and
 - c. Such imports meet the standards of quality and safety set out in the Directives, the Regulations, Directions 001/2006 and these Directions, as amended from time to time and as set out in any supplemental Directions given by the HTA from time to time.
109. The HTA may authorise any person to import or export tissues and / or cells directly from where procurement takes place to an organisation responsible for human application for immediate human application provided that: –
- a. It is satisfied that there is a case of emergency;
 - b. It is satisfied that it is necessary for clinical reasons;
 - c. It is satisfied that the tissues and / or cells concerned are specified for the purposes of article 6(5) of the parent directive; and
 - d. It receives a duly completed application form together with any and all supporting information requested by the HTA in support of the application.
110. The HTA may authorise any person to distribute tissues and / or cells directly from where procurement takes place to an organisation responsible for human application for immediate human application provided that: –
- a. It is satisfied that there is a case of emergency;
 - b. It is satisfied that it is necessary for clinical reasons;
 - c. It is satisfied that the tissues and / or cells concerned are specified for the purposes of article 6(5) of the parent Directive; and
 - d. It receives a duly completed application form together with any and all supporting information requested by the HTA in support of the application.

111. Establishments that import human tissues and / or cells from countries which are not EEA member states shall meet standards of quality and safety equivalent to those provided in the Regulations, the Directives, Directions 001/2006, these Directions, as amended from time to time and any supplemental Directions given by the HTA from time to time.
112. Establishments that export human tissues and / or cells to countries which are not EEA member states shall ensure that such exports comply with the Regulations, the Directives, Directions 001/2006, these Directions, as amended from time to time and any supplemental Directions given by the HTA from time to time.
113. The establishment, and any third party with whom the LH, or the DI on behalf of the LH, has a third party agreement, shall comply with the HTA's Code of Practice on Import and Export where it, or the third party on behalf of the LH, imports and / or exports tissues and / or cells for human application.
114. Where the LH, or the DI on behalf of the LH, has a third party agreement with a third party to import or export tissues and / or cells intended for human application on its behalf, the LH, or the DI on behalf of the LH, shall ensure that the third party agreement includes an obligation on the part of the third party to comply with the provisions of paragraphs **111** and **112** above.
115. The establishment, and any third party with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph 117 (a) below, must ensure that imported tissues and / or cells can be traced from the donor to the recipient and vice versa at all times. The establishment and any third party must comply with the traceability provisions of the Regulations, the Directives, Directions 001/2006 and these Directions, as amended from time to time.
116. Establishments that distribute and / or export tissues and / or cells for human application, or third parties distributing and / or exporting on behalf of the LH, shall comply with the provisions of paragraph **52** above.

Tissue establishments and third party relations

117. The establishment shall put in place and maintain written agreements with third parties ("third party agreements") whenever: –

- a. The third party procures, processes, tests, distributes, imports or exports tissues and / or cells on behalf of the LH; or
 - b. The third party supplies to the LH any goods or services which may affect the quality or safety of tissues and / or cells.
118. The LH shall ensure that any third party agreements entered into in accordance with paragraph **117 (a)** above complies with the following: –
- a. Article 24 of the parent directive, as set out in paragraphs 68 to 71 of Directions 001/2006, and these Directions, as amended from time to time;
 - b. Full address and named contact details of the third party together with the nature of the activity or activities to be performed on behalf of the LH by the third party;
 - c. Include provision on how often the third party agreement is to be reviewed and by whom;
 - d. Include an obligation on the part of the DI to notify of, and provide the third party with, copies of all regulatory alerts or other relevant communications from the HTA regarding serious adverse events and / or serious adverse reactions without delay in accordance with paragraph **12 (x)** above;
 - e. Include an acknowledgment by the third party that the requirements of any Directions given by the HTA from time to time including Directions 001/2006 and these Directions represent suitable practices in the course of the carrying on of the activity or activities under the third party agreement in accordance with paragraph **12 (y)** above;
 - f. Include an obligation on the part of the DI to provide the third party with copies of any Directions given by the HTA from time to time, which are relevant to the activity or activities carried out under the third party agreement, or relevant to the provision of goods or services under the third party agreement, as soon as possible after issue of the Directions by the HTA in accordance with paragraph **12 (z)** above;
 - g. The terms of the relationship between the establishment (LH, or the DI on behalf of the LH), and third party and the responsibilities of both must be specified as well as the protocols to be followed to meet the required performance

specifications in accordance with paragraph **22** above;

- h. Include any specific criteria that the activity or activities carried out by the third party on behalf of the LH must meet particularly in relation to quality and safety including disposal;
- i. Include an obligation on the part of the third party to put in place, maintain and comply with the SOPs required under the Regulations, Directions 001/2006 and these Directions, as amended from time to time;
- j. Include an obligation on the part of the third party to put in place and maintain a documented system that ensures the identification of every unit of tissue and / or cells at all stages of the activity or activities carried out by the third party on behalf of the LH in accordance with paragraph **25** above;
- k. Include an obligation on the part of the third party to ensure that the equipment and materials used by the third party are fit for purpose and that they are selected, maintained, and used in accordance with paragraph **33** above;
- l. Include an obligation on the part of the third party to ensure that relevant third party premises and the facilities of the third party are suitable for the activity or activities carried out on behalf of the LH and are provided and maintained in accordance with paragraphs **36–44** above;
- m. Where processing is carried out by a third party on behalf of the LH, the third party agreement must provide for the processing to take place in an environment with a specified air quality and cleanliness in accordance with paragraphs **39** to **42** above;
- n. Records must meet the confidentiality requirements laid down in the Regulations, the parent Directive, Directions 001/2006 and these Directions, as amended from time to time;
- o. Include an obligation on the part of the third party to retain the documents, procedures and records set out in accordance with paragraphs **45** and **46** above;
- p. Access to registers and data collected in pursuance of a third party agreement must be restricted to authorised persons and to the HTA in accordance with paragraphs

46 (i) and (j) and 59 to 65 above;

- q. Where the activity of processing is carried out by the third party on behalf of the LH, include an obligation on the part of the third party to comply with the processing and storage conditions set out in paragraphs **50** and **51** above;
- r. Include provision, where appropriate, as to how any test or diagnostic results will be communicated to the establishment including confirmation that the test or results applies to the correct sample;
- s. Where distribution is carried out by a third party on behalf of the LH, the third party agreement must ensure that the required conditions of distribution, recall and return are maintained and complied with in accordance with paragraph **52** above and that the transportation and external labelling requirements set out in paragraph 41 of Directions 001/2006, where appropriate, are complied with;
- t. Where distribution and / or export is carried out by the third party on behalf of the LH, the third party agreement must ensure that the requirements for final labelling and external labelling are maintained and complied with in accordance with paragraphs **53** to **55** above;
- u. Include an obligation on the part of the third party to comply with his / her duty regarding the disclosure of information and confidentiality and as set out in accordance with paragraphs **60** and **62** above;
- v. Include an obligation on the part of the third party to appoint a named individual within the third party's establishment to make the necessary arrangements to secure that the duty of the third party regarding the disclosure of information and confidentiality is complied with in accordance with paragraph **60** above;
- w. Include an obligation on the part of the third party to comply with Regulation 13 (2) of the Regulations to ensure that any information collected in pursuance of a third party agreement, and from which a donor, whether living or deceased, or recipient of tissues and / or cells may be identified is not disclosed other than in accordance with the terms of the Regulations in accordance with paragraph **63** above;

- x. Include an acknowledgement on the part of the third party that the duty of the third party regarding confidentiality and disclosure of information will continue to apply notwithstanding any termination of the third party agreement;
- y. Where the third party makes an authorised disclosure pursuant to any consent to disclosure given by the donor or recipient of the tissues and / or cells, whose identity would be disclosed, include an obligation on the part of the third party that such consent to disclosure must be in a format approved by the HTA in accordance with paragraph **65** above;
- z. Include an obligation that third parties who procure tissues and / or cells for human application on behalf of the LH will not procure tissues and / or cells other than in accordance with any Directions given by the HTA including Directions 001/2006 and these Directions in accordance with paragraph **66** above. This should include in particular an obligation on the part of the third party to comply with paragraphs 25–32 and 43–47 of Directions 001/2006;
- aa. Where the third party carries out the activity of procurement on behalf of the LH, include an obligation on the part of the third party to comply with the requirements of the Annex to the parent directive as set out in paragraph 14 of Directions 001/2006 and in accordance with paragraph **67** above;
- bb. Where the third party is a procurement organisation and / or an organisation responsible for human application of tissues and / or cells, include an obligation on the part of the third party to comply with the requirements of Articles 5 and 6 of the Second Commission Directive in accordance with paragraph **67** above;
- cc. Include an obligation to retain records, and notify the establishment, the HTA, and other relevant tissue establishments as appropriate, of any serious adverse event that may influence the quality or safety of tissues and / or cells, and any serious adverse reaction which may influence or be linked to the quality or safety of tissues and / or cells, in accordance with paragraphs **67** and **98** to **99** above;
- dd. Where the third party carries out the activity of distribution on behalf of the LH, include an obligation on the part of the third party to comply with the provisions of paragraph

- 52** above as appropriate in respect of any application to the HTA for direct distribution of specified tissues and / or cells directly from where procurement takes place to an organisation responsible for human application for immediate human application, in accordance with paragraph **69** above;
- ee. Where the third party is an organisation responsible for human application, include an obligation on the part of the third party to retain the information on the minimum donor / recipient data required under the Second Commission Directive in accordance with paragraph **71** above;
 - ff. Where the third party carries out the activity of processing on behalf of the LH, include provision to ensure that in the event of termination of activities for whatever reason (including closure of the third party establishment), tissues and / or cells are transferred (subject to the consent of the donor) to the licensed establishment or another licensed establishment or establishments in accordance with paragraph **77** above;
 - gg. Include an obligation on the part of the third party to have effective and accurate systems to uniquely identify and label all tissues and / or cells received and distributed in order to comply with the provisions of the Second Commission Directive in accordance with paragraph **80** above;
 - hh. Include provision in relation to the transfer of minimum information referred to in paragraphs **71, 81** and **83** above;
 - ii. Include an obligation on the part of the third party to allocate a single European identifying code to all donated material, at all stages of the activity or activities carried out by the third party, to ensure proper identification of the donor, the traceability of all donated material and to provide information on the main characteristics and properties of tissues and / or cells. The code to incorporate, at least, the information set out in paragraph **83** above as required by the Second Commission Directive;
 - jj. Include an obligation on the part of the third party to ensure that information collected under a third party agreement, including the minimum information referred to in paragraphs **71, 81** and **83** above, is available for the purpose of tracing donations and identifying information is disclosed to the establishment for the purpose of tracing a

donation from donor to recipient, or vice versa in accordance with paragraph **86** and **87** above;

- kk. Include an obligation on the part of the third party to maintain the registers and information required under paragraph 57 of Directions 001/2006 as amended by paragraph **88** above and in accordance with paragraph **90** above;
- ll. Include an obligation on the part of the third party to ensure that such registers and information as referred to in paragraph **90** above are available for inspection at all times by a duly authorised person or persons on behalf of the HTA in accordance with paragraph **91** above;
- mm. Include an obligation on the part of the third party to furnish an annual report to include a report of its activities to the establishment as required by paragraph **92** above;
- nn. Include provision that in the event of the termination of activities, for whatever reason (including closure of the third party establishment), the third party must ensure that the registers, documentation, records and information retained pursuant to Directions 001/2006 and these Directions, as amended from time to time, are transferred to another licensed establishment or establishments in accordance with paragraph **96** above;
- oo. Include an obligation on the part of the third party to comply with the parent directive, Articles 5 (1) and 6 (1) of the Second Commission Directive, and Regulation 15 of the Regulations regarding the identification, investigation, reporting, recording and notification of serious adverse events and / or serious adverse reactions in accordance with paragraphs **98** and **99** above;
- pp. Where the third party carries out the activity of distribution on behalf of the LH, include an obligation on the part of the third party to provide information to any organisation responsible for human application of tissues and / or cells about how that organisation should report serious adverse reactions in accordance with paragraph **99 (b)** above;
- qq. Include an obligation on the part of the third party to notify the establishment and / or the HTA of the actions taken by the third party, with respect to other implicated tissues and / or cells that have been distributed for human application in accordance with paragraph **99 (d)** above;

- rr. Include an obligation on the part of the third party to report relevant information to personnel within the third party establishment and to the establishment and other establishments engaged in the procurement, testing, processing, storage and distribution of tissues and / or cells for human application and the HTA in order to facilitate traceability and ensure safety and quality controls;
- ss. Include an obligation on the part of the third party to put in place and maintain a SOP for the identification, investigation, reporting, recording and notification of serious adverse events and / or serious adverse reactions in accordance with the relevant provisions of paragraph 60 of Directions 001/2006 and in accordance with the relevant provisions of paragraph **100** above;
- tt. Include an obligation on the part of the third party to enable such investigation and control measures as appropriate to be carried out by the HTA in accordance with paragraph **104** above. The HTA's statutory powers, including its powers to enter, inspect and search relevant third party premises and to observe the carrying-on of activities carried out under the third party agreement at relevant third party premises, are set out in the Regulations;
- uu. Include an obligation on the part of the third party to have an accurate, rapid and verifiable recall procedure which will enable it to recall from distribution any product which may be related to a serious adverse event and / or a serious adverse reaction, and complies with paragraphs **52, 106** and **107** above;
- vv. Where a third party imports tissues and / or cells on behalf of the LH, include an obligation on the part of the third party to comply with the provisions of paragraph 64 of Directions 001/2006 as amended by paragraph **108** above;
- ww. Where the third party imports, exports or distributes tissues and / or cells on behalf of the LH, include an obligation on the part of the third party to obtain approval from the HTA in accordance with paragraphs **109** and **110** above to import, export or distribute directly from where procurement takes place to an organisation responsible for human application for immediate human application;

- xx. Where the third party imports or exports tissues and / or cells on behalf of the LH, include an obligation on the part of the third party to comply with the HTA's Code of Practice on Import and Export in accordance with paragraph **113** above;
- yy. Where the third party imports tissues and / or cells from countries which are not EEA member states on behalf of the LH, include an obligation on the part of the third party that all such imports meet standards of quality and safety equivalent to those provided in the Regulations, the Directives, Directions 001/2006, these Directions, as amended from time to time and any supplemental Directions given by the HTA from time to time, in accordance with paragraph **114** above;
- zz. Where the third party exports tissues and / or cells on behalf of the LH, include an obligation on the part of the third party that all exports comply with the Regulations, the Directives, Directions 001/2006, these Directions, as amended from time to time and any supplemental Directions given by the HTA from time to time in accordance with paragraph **114** above;
- aaa. Where the third party imports tissues and / or cells on behalf of the LH, include an obligation on the part of the third party to ensure that imported tissues and / or cells can be traced from the donor to the recipient and vice versa, in accordance with paragraph **115** above;
- bbb. Where procurement is carried out by the third party on behalf of the LH, include an obligation on the part of the third party to produce a report to the establishment in accordance with paragraph 34 of Directions 001/2006;
- ccc. Include provision to ensure that in the event of termination of the activity or activities for whatever reason (including closure of the third party establishment), tissues and / or cells are transferred (subject to the consent of the donor) to the licensed establishment or another licensed establishment or establishments;
- ddd. Include an obligation on the part of the third party to notify of, and provide users of tissues and / or cells with, copies of all regulatory alerts or other relevant communications from the HTA regarding serious adverse events and / or serious adverse reactions without delay;
- eee. Technical aspects of the agreement must be drawn up by competent persons, suitably knowledgeable in the field

and the responsibilities of third parties must be non-delegatable;

- fff. Include identification of which party is responsible for obtaining consent and carrying out donor selection and testing in accordance with Directions 001/2006 and the maintenance and retention of documentation and records required by Directions 001/2006 and these Directions as amended from time to time; and
 - ggg. The procedure for complaints must be specified including how complaints will be handled.
119. The LH shall ensure that any third party agreements entered into in accordance with paragraph **117 (b)** above complies with the following: –
- a. Paragraph 118 (a), (b), (c), (e), (f), (g), (h), (n), (p), (u) to (y) inclusive, (cc), (ee), (rr), (ss), (tt), (uu) and where appropriate (d), (j), (k), (l), (jj), (ddd), (eee) and (fff) above; and
 - b. Include an obligation to have effective and accurate systems to identify and label all products.
120. To enable the DI to comply with his / her duty to secure compliance with the conditions of third party agreements, the third party shall afford the DI such access to its facilities, relevant third party premises, its documentation and records as is necessary to enable the DI to comply fully with his duty under Regulation 12 of the Regulations and as set out in paragraph **11** above.
121. It shall be the responsibility of the third party to make all necessary arrangements to ensure that all information which is collected under a third party agreement: –
- a. Is available for the purpose of tracing donations;
 - b. Is kept up-to-date and corrected without delay, where any discrepancy relating to such information is identified; and
 - c. Is held securely and subject to safeguards against unauthorised additions, deletions, modifications or transfer of information.
122. It shall be the responsibility of the third party to ensure that any information collected under a third party agreement, and from which a donor, whether living or deceased, or recipient of tissues and / or cells may be identified, is not disclosed other than in accordance with the Regulations including disclosures

to a LH or a person to whom the licence applies for the purposes of his / her functions under a licence.

Termination agreements and termination of activities

123. All agreements in relation to the termination of the licensed activity or activities (including closure of the establishment or third party establishment with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph **117 (a)** above) (“termination agreements”) shall, as a minimum, comply with the following: –
- a. Include the procedures to be adopted in accordance with Article 21 (5) of the parent directive, to include traceability data and material concerning the quality and safety of tissues and / or cells in accordance with paragraph **24** above;
 - b. Include provision to secure that all records, including raw data, critical to safety and quality, be retained and maintained in accordance with paragraph **46** above, including the transfer of such records and raw data to another licensed establishment or establishments;
 - c. Include an acknowledgement of the subsisting duty of the DI and / or third party, including former DIs and third parties, in accordance with paragraph **64** above;
 - d. Include an obligation to retain the documentation and records required to be kept under the Regulations, the Directives, Directions 001/2006, and these Directions, as amended from time to time, to include the documentation and records referred to in paragraphs **45, 46** and **70 to 72** above;
 - e. Include an obligation to ensure that tissues and / or cells are transferred (subject to the consent of the donor) without delay to another licensed establishment or establishments following termination of activities;
 - f. Include provision to secure compliance with the traceability and coding provisions of the Regulations, the Directives, Directions 001/2006 and these Directions, as amended from time to time, including but not limited to paragraph 54 of Directions 001/2006, as amended by these Directions, paragraph 55 of those Directions and paragraphs **79, 81, 82** and **83** of these Directions;
 - g. Include provision in relation to the transfer of the minimum information and coding information required to

be retained under the provisions of the Second Commission Directive and these Directions to another licensed establishment or establishments following termination of the activity or activities, including the information referred to in paragraphs **70, 71, 81, 83** and **84** above;

- h. Include provision in relation to the transfer of the registers retained in accordance with paragraph 57 of Directions 001/2006 as amended by these Directions, and by paragraphs **88** to **90** of these Directions to another licensed establishment or establishments following termination of activities, or alternatively transfer to the HTA;
- i. Include provision in relation to the transfer of any records or information retained in accordance with paragraphs **98** to **100** above to another licensed establishment or establishments following termination of activities, or alternatively transfer to the HTA;
- j. Include provision for the transfer of any third party agreement or agreements made between the LH, or the DI on behalf of the LH and any third party in accordance with paragraph **117** above to another licensed establishment or establishments, following termination of activities, or alternatively transfer to the HTA;
- k. 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 in accordance with paragraphs **60, 64, 120** and **121** above;
- l. Prior to the transfer of any tissues and / or cells, the establishment and any third party with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph **117 (a)** above, shall carry out an audit of stored tissues and / or cells and shall ensure that all discrepancies are resolved. The establishment shall furnish a copy of the report of the audit to both the establishment to which the tissues and / or cells are being transferred (receiving establishment) and the HTA; and
- m. The establishment shall ensure that the transfer of tissues and / or cells is carried out under conditions that ensure that the integrity and quality of the tissues and / or cells is maintained.

124. The establishment, and any third party with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph **117 (a)** above, shall keep the HTA informed of any termination of activities (including closure of the establishment or third party establishment) and / or transfer of tissues and / or cells, including when the termination or transfer will occur and to where the tissues and / or cells will be moved. The establishment and any third party shall keep the HTA up to date at all times with the progress of the termination/transfer.
125. The establishment, and any third party with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph **117 (a)** above, shall provide the HTA with the name of a contact person who will deal with all queries following the termination of activities or closure of the establishment or third party establishment. This contact person must also deal with any queries from the receiving establishment.
126. The establishment, and any third party with whom the LH, or the DI on behalf of the LH, has a third party agreement in accordance with paragraph **117 (a)** above, shall follow the HTA's guidance on closure procedures for establishments and complete the HTA's Closure Pro forma Form as issued from time to time.

Miscellaneous

127. These directions are made by the HTA.

Dated the 5 day of July 2007.

Signed:



Adrian McNeil
Chief Executive
Human Tissue Authority

ANNEX A

Annex IV Second Commission Directive 2006/86/EC

NOTIFICATION OF SERIOUS ADVERSE EVENTS

PART A

**Rapid Notification for
Suspected Serious Adverse Events**

| | | | | |
|--|-------------------------------|-------------------|-------------|-----------------|
| Tissue establishment: | | | | |
| Report identification: | | | | |
| Reporting date (year/month/day): | | | | |
| Date of serious adverse event (year/month/day): | | | | |
| Serious adverse event, which may affect quality and safety of tissues and / or cells due to a deviation in: | Specification | | | |
| | Tissues and / or cells Defect | Equipment failure | Human error | Other (specify) |
| Procurement | | | | |
| Testing | | | | |
| Transport | | | | |
| Processing | | | | |
| Storage | | | | |
| Distribution | | | | |
| Materials | | | | |
| Others (<i>specify</i>) | | | | |

PART B

Conclusions of Serious Adverse Events Investigation

| |
|---|
| Tissue establishment: |
| Report identification: |
| Confirmation date (<i>year/month/day</i>): |
| Date of serious adverse event (<i>year/month/day</i>): |
| Root cause analysis (details): |
| Corrective measures taken (details): |

ANNEX B

Annex III Second Commission Directive 2006/86/EC

NOTIFICATION OF SERIOUS ADVERSE REACTIONS

PART A

Rapid Notification for Suspected Serious Adverse Reactions

| |
|---|
| Tissue establishment: |
| Report identification: |
| Reporting date (<i>year/month/day</i>): |
| Individual affected (recipient or donor): |
| Date and place of procurement or human application (<i>year/month/day</i>): |
| Unique Donation identification number: |
| Date of suspected serious adverse reaction (<i>year/month/day</i>): |
| Type of tissues and / or cells involved in the suspected serious adverse reaction: |
| Type of suspected serious adverse reaction(s): |

PART B

Conclusions of

Serious Adverse Reactions Investigation

| |
|---|
| Tissue establishment: |
| Report identification: |
| Confirmation date (year/month/day): |
| Date of serious adverse reaction (year/month/day): |
| Unique Donation identification number: |
| Confirmation of serious adverse reaction (Yes / No): |
| Change of type of serious adverse reaction (Yes / No) If Yes, Specify: |
| Clinical outcome (if known): <ul style="list-style-type: none">- Complete recovery- Minor sequelae- Serious sequelae- Death |
| Outcome of the investigation and final conclusions: |
| Recommendations for preventive and corrective actions: |

ANNEX C

DEFINITIONS

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

| | |
|--------------------------|---|
| Autologous graft: | Means tissue or cells removed from and applied in the same person within the same surgical procedure. |
| Blood: | Means whole human blood collected from a donor and processed either for transfusion or for further manufacturing. |
| Blood component: | Means a therapeutic constituent of human blood (red cells, white cells, platelets and plasma) that can be prepared by various methods, but does not include lymphocytes intended for use for the purpose of haematopoietic stem cell transplantation. |
| Cells: | Means individual human cells or a collection of human cells when not bound by any form of connective tissue, including cell lines grown outside the human body but not including: – <ol style="list-style-type: none">Gametes;Embryos outside the human body; orBlood and blood components. |
| Distribution: | Means transportation and delivery of tissues or cells intended for human applications. A person who, from any premises, controls the provision of services for transporting tissue or cells is to be taken to distribute tissue or cells on those premises. |
| Donation: | means donating human tissues or cells intended for human applications. |
| Donor: | means every human source, whether living or deceased, of human cells or tissues. |

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

recipient of tissue or cells, which may be associated with the procurement or human application of tissue or cells and which is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity.

- Storage:** Means maintaining tissue or cells, whether by preservation or in any other way, for more than 48 hours.
- Third Party:** Means a person with whom a LH, or the DI on behalf of the LH, has a third party agreement.
- Third Party Agreement:** Means an agreement in writing between a LH, or the DI on behalf of the LH, and another person which is made in accordance with any Directions given by the HTA for the purpose of securing compliance with specified requirements of the Regulations and Directives, and under which the other person: –
- a. Carries on a licensed activity (other than storage), on behalf of the LH i.e. procures, processes, tests, distributes, imports 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.
- Relevant Third Party Premises:** Means any premises (other than premises to which the licence relates): –
- a. On which a third party procures, tests, processes or distributes, or to which a third party imports or from which a third party exports, 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:

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

—

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