



Human Tissue Authority

Guidance document for establishments working with
Umbilical cord blood

29 November 2010

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Introduction

1. This document is intended to provide clear guidance to establishments licensed by the Human Tissue Authority (HTA) to undertake activities related to the procurement, testing, processing, storage, distribution, import and export of umbilical cord blood cells. Such licences are issued under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (the Q&S Regulations).
2. A number of establishments which were originally licensed to procure and store umbilical cord blood have expressed an interest in expanding their activities to include work with other tissues, including umbilical cord tissue. Where relevant, the guidance also covers these tissues.
3. The advice in the document will concentrate on areas which are specific to umbilical cord blood and related tissues. It is, however, important that establishments working with umbilical cord blood are familiar with all aspects of licences for the use of tissues and cells for treatment (human application).
4. The information in the document will raise awareness of the HTA regulatory requirements and clarify the HTA's position in relation to licensable activities relating to umbilical cord blood. This document supplements and adds further explanations to the information in HTA Directions 003/2010. This will assist establishments undertaking activities involving umbilical cord blood and related tissues to meet the HTA regulatory requirements.
5. Internally, the document will provide a clear basis for HTA staff interacting with stake holders from the umbilical cord blood sector. This will ensure the consistency of the advice offered to external organisations.

The umbilical cord blood sector and the role of the Designated Individual

6. The umbilical cord blood sector includes a range of establishments which handle umbilical cord blood and umbilical cord tissue. These establishments may undertake any of the following activities licensed by the HTA:
 - Procurement
 - Donor testing
 - Processing
 - Storage
 - Distribution
 - Import
 - Export

7. The establishments may handle umbilical cord blood and cord tissue which has been:
 - procured in the United Kingdom (UK)
 - procured in countries which are member states of the European Economic Area (EEA) and transported to tissue establishments in the UK; further details of the countries comprising the EEA are given in paragraph 67 of this document.
 - procured in countries which are not member states of the EEA ('non-EEA member states') and imported into the UK

8. Tissues and cells which are procured within an EEA member state fall under the regulatory requirements of the European Union Tissues and Cells Directives. Tissues and cells which are procured in non-EEA states are covered by the quality and safety standards which apply in those particular countries. However, for these materials to be imported into the UK, the quality and safety of the tissues and cells must comply with the standards set out in HTA Directions 003/2010. Once the tissues and cells enter the UK, the standards for donor testing, processing, storage and distribution must also be in accordance with HTA Directions 003/2010.

Responsibilities of the Designated Individual, Licence Holder and/or Corporate Licence Holder contact

9. The Q&S Regulations set out the responsibilities of the Designated Individual (DI) as well as the qualifications which are required for the role. Establishments have to apply for a licence to the HTA. The HTA assesses this application and evaluates the suitability of the DI. The DI must have a diploma, certificate or other evidence of formal qualifications in the fields of medical or biological sciences awarded on completion of a university course of study, or other course of study recognised in the United Kingdom as equivalent, or be otherwise considered by the Authority to be suitably qualified on the basis of academic qualifications and practical experience, and must have at least two years practical experience in the relevant fields.
10. The DI must ensure:
 - that the practices are suitable
 - that the premises are suitable
 - that other persons working under the licence are suitable
 - that the conditions of the licence are complied with
 - that the conditions of third party agreements are complied with, and
 - that all information relating to licensable activities is available for tracing donations, is up-to-date and correct, and is held securely.
11. As set out in standard condition 1 in Annex B of human application licences, DIs must complete HTA accredited training to the HTA's satisfaction within twelve months of assuming their duties. The DI can also nominate Persons Designated under the licence to whom he can delegate specific operational responsibilities.
12. An HTA licence can be held by an individual or a corporate body. The Licence Holder (LH) is responsible for paying the licence fee and ensuring that all HTA Directions and standards relating to third party agreements are complied with. If the Licence Holder is a corporate body, the HTA requires that a person is nominated to act as a point of contact for the corporate licence. The HTA terms this person the Corporate Licence Holder contact and they should be in a position to act as a representative of the corporate body. The LH must ensure that a suitable DI is in place at all times.
13. The LH must also be in a position to apply to the HTA to replace the DI with another individual, if required. This situation might arise if the DI was

away for a long period of time, for example four weeks, or was unable for various reasons to perform their duties, and would require an assessment by the HTA of the suitability of the proposed DI.

14. The DI at an umbilical cord blood establishment is required to comply with the regulatory requirements set out in the Directions issued from time to time by the HTA.

DI and LH responsibilities in relation to third parties

15. The DI and LH at umbilical cord blood establishments may have arrangements in place with other organisations or individuals to provide a service that supports the work of the establishment. For example, the establishment may rely on a third party to collect, test or process the umbilical cord blood. Similarly, establishments will have arrangements in place with transport companies, companies who service and maintain equipment and suppliers of equipment. The Q&S Regulations require all such arrangements between the tissue establishment and other organisations within the UK to be underpinned by a third party agreement (TPA). In cases where both organisations are licensed by the HTA, a service level agreement (SLA) is appropriate.
16. The DI and LH must ensure that the agreements they have with other organisations or individuals are appropriate and comply with the standards set out in HTA Directions 003/2010. Further information about TPAs and SLAs is included in paragraphs 83-89 of this document under the heading 'Third Party Agreements'.

Serious Adverse Events and Reactions

17. The DI is responsible for reporting Serious Adverse Events (SAEs) and Serious Adverse Reactions (SARs) to the HTA, as set out in paragraphs 171-187 of HTA Directions 003/2010. The initial notification to the HTA should be given within 24 hours of the discovery or determination of the SAE or SAR by the licensed establishment. Agreements with third parties and end users should include a requirement to report to the licensed establishment within 24 hours of their discovery of SAEs or SARs.
18. As set out in paragraph 90 of this document, the procurement of umbilical cord blood must only be carried out under an HTA licence or in pursuance of a TPA. If procurement occurs outside the HTA licensing framework, the DI is responsible for reporting the unlawful procurement to the HTA as an SAE.

Procurement

19. HTA Directions 003/2010 define procurement to be a process by which tissues or cells are made available. This includes consent, donor selection, preparation and distribution of umbilical cord blood collection kits, as well as the actual collection of the umbilical cord blood.
20. In this document, the mother of the child whose umbilical cord blood is being collected is treated as the donor. For situations where a surrogate mother is involved, establishments should seek legal advice as to the rightful ownership of the umbilical cord blood for both consent and contractual purposes.

Consent

21. The requirements for consent are set out in paragraphs 72-77 of HTA Directions 003/2010. As required by the HTA's Code of Practice on Consent, consent must be both valid and appropriate. The DI needs to be assured that all persons seeking consent for the donation of umbilical cord blood or tissue have received appropriate training in taking consent in accordance with the Human Tissue Act 2004 (HT Act), and that this training is documented. This requirement applies to staff within the establishment and to those working under third party agreements. The consent provisions of the HT Act do not apply to material which has been imported. Nonetheless, the HTA code of practice on Consent requires the DI to obtain assurance that human tissue which is imported into the UK has been obtained with valid consent in accordance with local practice in the source country.
22. Appropriate consent is defined in the HTA code of practice on Consent in terms of the person who may give consent. In the case of the procurement of umbilical cord blood, the mother (the donor) would normally give consent for the donation. When umbilical cord blood samples are procured outside the UK, local requirements in relation to consent for processing and storage may have to be taken into account, but the consent for the donation should normally be given by the mother.
23. Valid consent is defined in the HTA code of practice on Consent, which states that consent must be given voluntarily, by an appropriately informed person who has the capacity to agree to the activity in question.
24. It is not sufficient to assume that a donor is giving consent because they have sought out an umbilical cord blood collection service. Potential donors must be fully informed of all aspects of the licensable activities to

ensure that the risks and benefits of umbilical cord blood collection are fully explained and their expectations are managed. The information regarding consent must include, but is not limited to, the following elements:

- who can lawfully procure the umbilical cord blood and the consequences of unlawful procurement
- what will happen to the umbilical cord blood once collected
- how the procurement will be carried out e.g. *in utero*, or *ex utero*; but taking into account the information set out in paragraph 35 of this document
- the biological tests which will be carried out, the manner in which the results will be communicated and the possible consequences of a positive test
- whether umbilical cord blood will be stored on a public/private and autologous/allogeneic basis
- whether or not a repeat sample from the donor is required for testing after an interval of 180 days
- what information will be recorded and held by the licensed establishment
- that consent can be withdrawn
- the legal requirements for procurement.

25. It should be noted that the HTA's remit does not include contractual obligations between licensed umbilical cord blood establishments and clients. Consent should be sought and documented separately from contractual obligations.

Donor selection

26. The requirements for donor selection, evaluation and testing for all tissues and cells are set out in paragraphs 78-94 and Annexes B & C of HTA Directions 003/2010.

27. Licensed establishments must put in place policies or procedures to describe whether umbilical cord blood is to be stored and released on an allogeneic or autologous basis, and the requirements for testing prior to release. This should include a policy on what would happen if umbilical cord blood stored for autologous use, and meeting only the standards for testing required for autologous use, was requested to be released on an allogeneic basis. Paragraphs 43-54 of this document set out in greater

detail the requirements for testing of umbilical cord blood samples which are intended for autologous and allogeneic treatment.

28. Umbilical cord blood intended solely for autologous use, and tested only at the time of donation, must be labelled 'for autologous use only'. If there is any possibility of the umbilical cord blood being released for use on an allogeneic basis, the testing must comply with the requirements set out in paragraphs 91-92 and Annex B of HTA Directions 003/2010 for allogeneic donors. A clinician may, however, decide that it is appropriate to use umbilical cord blood meeting only the standards for testing required for autologous use, for the allogeneic treatment of life threatening conditions.

Procurement kits and consumables

29. Equipment used for procurement may impact on the quality and safety of the umbilical cord blood collected. DIs must ensure compliance with the following in relation to procurement equipment:

- paragraphs 26, 27, 39-43, and 46 of HTA Directions 003/2010;
- licensing standards GQ1j, GQ4j, and applicable sub-standards under PFE5

30. Records must be retained of the batch and expiry of consumables or equipment used during the procurement process. Consideration should be given to recording these numbers in such a way to facilitate a recall if required.

31. Where an establishment distributes procurement equipment in kit form, the DI should ensure that:

- any procurement instructions within the kit make it clear that a procurer must be trained and acting in accordance with a third party agreement with the licensed establishment, and that
- robust procedures are in place to establish traceability from the point of distribution of the kit.

Collection of Umbilical Cord Blood

32. The collection of umbilical cord blood is covered by paragraphs 95-110 of HTA Directions 003/2010, describing procurement procedures for tissues and cells.

33. As set out in paragraph 95 of HTA Directions 003/2010, the collection of umbilical cord blood must be carried out by registered healthcare professionals. They must have the necessary experience for undertaking the procurement procedure, either evidenced by their general job responsibilities or by having completed a documented training programme as agreed by the DI, with the input of a clinical team specialising in umbilical cord blood procurement. They must be acting either under an HTA licence or a third party agreement with an HTA-licensed establishment. Procurement by an untrained person, or by a person acting outside the licensing framework, is unlawful.
34. DIs of private umbilical cord blood banks should take particular care to ensure that potential donors do not see the procurement kit as a 'Do It Yourself' kit. DIs should implement robust procedures to make potential donors aware of the licensing framework, the persons who can lawfully collect umbilical cord blood, and the potential consequences of failure to comply with these requirements. This information should be provided to potential donors as part of the informed consent process.
35. The HTA endorses guidance from the Royal College of Obstetricians and Gynaecologists which states that, in order 'to maximise safety for the mother and infant, collection should be made from the *ex utero* separated placenta'. Where establishments choose to undertake *in utero* collections against this advice, they must carry out a risk assessment of this practice and procurers must be given specific training in the *in utero* collection procedure.
36. Risk assessments should be undertaken of all premises where collection is to be carried out, even those in hospitals or birthing facilities. Where licensed or relevant third party premises are routinely used for umbilical cord blood collection, risk assessments do not have to be carried out prior to each individual collection, but they should be updated annually or whenever there is a change to the premises that may affect the quality and safety of the tissues and cells being collected.
37. HTA Directions 003/2010 indicate that, if third party premises (including hospitals, birthing facilities and home births) are used on an *ad hoc* basis, a risk assessment of the facilities must be carried out prior to each collection of umbilical cord blood. Training should be provided to procurers in how to assess premises for risks. This training should include what to do if the premises are unsuitable. Risk assessments should document the details of the location at which the umbilical cord blood was procured, e.g. 'room 123 of NHS Hospital' rather than simply 'NHS Hospital'. As set out in paragraph 108 of HTA Directions 003/2010,

the organisation performing the procurement of tissues or cells must produce a procurement report, which is passed on to the tissue establishment. This report must include the environmental conditions at the procurement facility, a description of the physical area where procurement took place and a risk assessment to determine suitability of the premises for *ad hoc* procurement.

38. The procurer must record any adverse event or reaction and advise the DI as soon as practicable. The DI is then responsible for advising the HTA of serious adverse events or reactions. Again, training should be provided to procurers to ensure that adverse events or reactions are reported and managed appropriately.
39. Packaging, labelling and transport are all part of the licensable activity of distribution; requirements for these activities are set out in HTA Directions 003/2010. A third party procurer who packages and labels umbilical cord blood to be collected by a courier is carrying out this licensable activity on behalf of the licensed establishment. DIs must ensure that procedures and training are supplied to any third party procurer responsible for packaging and labelling of cells prior to transport.
40. Parents should not be expected to package or label cells prior to transport. DIs must ensure that the training programme and procedures for procurers covers these aspects.
41. In particular, DIs of umbilical cord blood establishments should remember that third party phlebotomists often work for more than one licensed establishment. Robust procedures must be implemented to ensure that a procurer, working under a particular licence, is working to the procedures, standards and expectations set down by that particular licensed establishment.
42. As set out in paragraph 89 of this document, the DIs of umbilical cord blood establishments should audit third parties responsible for procurement so that they have direct knowledge of the working practices which are followed by any third party with which a TPA is in place.

Testing

43. The DI should ensure that testing is carried out as set out in Annex B of HTA Directions 003/2010, by suitable laboratories using CE marked kits. The testing may be conducted by the licensed establishment itself, or in

pursuance of a TPA. The DI should obtain an assurance that any testing laboratory in the United Kingdom is licensed by the HTA. In other EEA member states, the testing laboratory should be accredited by the relevant Competent Authority. The DI should check the accreditation status of a laboratory before accepting donor test results.

44. As with all tissues and cells intended for patient treatment, donors of umbilical cord blood must be tested for evidence of infection with Human Immunodeficiency Virus (HIV), hepatitis viruses B and C (HBV, HCV), syphilis and, in certain circumstances, Human T-lymphotropic virus Type I (HTLV-I). These tests are mandatory before the storage or culturing of tissues and cells intended for autologous or allogeneic transplant.
45. Annex B of HTA Directions 003/2010 requires biological tests on the donor, but new-born babies have an undeveloped immune system; most antibodies present in the umbilical cord blood will be the result of passive immunity from the mother. Testing of the mother's blood fulfils the requirement for antibody tests on the donor. The maternal blood sample for antibody testing must be taken at the time the umbilical cord blood is procured, or at least within seven days of the time of donation.
46. Annex A of HTA Directions 003/2010 sets out the requirement to select allogeneic living donors on the basis of their medical and behavioural history. It is good practice to obtain this information and the donor's consent for donation well in advance of the procurement; doing this while the mother is in labour is not appropriate.
47. In cases where the mother is likely to test positive she must be made aware of the chance of the umbilical cord blood being infected, and how this will affect its storage and use. This will allow her to make a fully informed decision as to whether or not to consent to the procurement. The HTA recommends that DIs advise mothers about the umbilical cord blood collection Frequently Asked Questions for parents on the HTA website.
48. In order for the umbilical cord blood to be released for allogeneic use, including the treatment of other members of the donor's family, where the tissue is stored for more than six months prior to use, Annex B of HTA Directions 003/2010 requires that repeat sampling and serological testing of the donor is carried out after an interval of 180 days following donation. As it may be impractical to obtain a blood sample from the donor at this time, establishments may wish to consider conducting a validated Nucleic Acid Amplification Technique (NAT) test on a sample

taken at the time of donation, as this will remove the requirement for repeat testing, including the requirement for repeat testing for syphilis.

49. In summary, the mandatory testing requirements for all donors of umbilical cord blood are as follows:

Table 1. Testing requirements at the time of donation of umbilical cord blood:

Pathogen	Serology Testing at time of donation
HIV	Anti-HIV-1,2
HBV	HBsAg and anti-HBc
HCV	Anti-HCV-Ab
<i>T. pallidum</i> (syphilis)	Anti- <i>T. pallidum</i>

The mandatory additional testing requirements when the cells are stored and intended for allogeneic use are summarised below:

Table 2. Testing requirements when umbilical cord blood cells are stored for allogeneic use:

Pathogen	Serology Testing after 180 days	Alternative Analytical Testing
HIV	Anti-HIV-1,2	HIV-NAT
HBV	HBsAg and anti-HBc	HBV-NAT
HCV	Anti-HCV-Ab	HCV-NAT
<i>T. pallidum</i> (syphilis)	Anti- <i>T. pallidum</i>	Not required

50. HTLV-I antibody testing should be performed on the maternal blood at the time of donation for donors living in, or originating from, high-incidence areas or with sexual partners originating from those areas or where the donor's parents originate from those areas. Again, HTLV-I-NAT testing at the time of donation removes the requirement for a repeat test 180 days after donation.
51. The HTA regards it as good practice to conduct the mandatory serological testing of the mother's blood at the time of donation, together with NAT testing on samples of both maternal and umbilical cord blood. The NAT tests remove the requirement for a repeat test of the donor's blood 180 days after procurement. The HTA recommends that both maternal and umbilical cord blood samples are retained for biological marker tests in the future. All mandatory testing must be completed prior to the release of a donation for end use.

52. Positive results from the tests of the maternal blood sample do not necessarily mean that the umbilical cord blood is contaminated. Annex B of HTA Directions 003/2010 allows the use of these samples if there is no evidence of infection of the baby through physical examination and analytical tests; currently, the most appropriate procedure is to conduct NAT tests on a sample of umbilical cord blood to establish the status of the donation. Establishments are therefore advised to collect umbilical cord blood in a manner that allows small separate samples to be able to be tested in the event of positive maternal test results.
53. When maternal tests are positive, the umbilical cord blood unit should be stored in quarantine and its acceptance or rejection for allogeneic use should be based on a documented risk assessment using the NAT testing results of the umbilical cord blood unit, or other test, to ensure that the donation meets the requirements set out in HTA Directions 003/2010.
54. Where matched stored umbilical cord blood for allogeneic use is brought into the UK from other countries for the treatment of life threatening conditions, the donations are not always fully tested in accordance with the specifications given above. Where repeat testing or NAT testing has not taken place, additional NAT tests must be carried out wherever there is access to blood from the original maternal donation sample or to a sample of the unprocessed cord blood. Exceptionally, if no additional testing is possible, a risk assessment should be carried out by the clinician intending to use the umbilical cord blood, in order to determine whether the material is suitable for release under these circumstances, and the cells should be stored in quarantine.

Processing

55. The processing of umbilical cord blood must be carried out in a manner which meets the standards set out in the HTA legal Directions covering all tissues and cells which are to be used for treatment (human application).
56. HTA Directions 003/2010 provide information to establishments about the requirements for processing tissues and cells. These include the requirement that, where tissues or cells are exposed to the environment during processing, 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 colony counts.

57. It should be recognised that closed systems are frequently used for the processing of umbilical cord blood samples prior to storage. Other tissues, such as umbilical cord itself, are usually more exposed to the environment during processing, and greater attention has to be paid to the environmental conditions. DIs should take steps to assure themselves that the background environment is suitable for the processing of the specific tissue type.
58. The critical processing procedures must be validated and must not render the tissues 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 or cells supplied by the establishment. All procedures must be documented in Standard Operating Procedures (SOPs) which must conform to the validated method.

Storage

59. The storage of umbilical cord blood must meet the HTA standards for all tissues and cells which are intended to be used for treatment (human application).
60. The cryopreservation of the cells, utilising storage in tanks of liquid nitrogen, can be achieved by holding the cells in the liquid phase or the vapour phase within the tank. The former is regarded as less likely to be affected by transient warming events whereas the latter is regarded as posing a lower risk of transmission of contaminant viruses between samples. A risk assessment of possible cross contamination should be conducted prior to the immersion of cells in liquid nitrogen for storage.
61. Establishments should carry out risk assessments and define policies on the storage of donations for which complete testing data are not available, or for which the donor's complete behavioural history is not known. Such donations should be regarded as potentially hazardous, as they represent a potential source of cross-contamination for donations which are fully tested and released for use.
62. As set out in paragraph 120 of HTA Directions 003/2010, tissues and cells must be quarantined until these, along with the associated documentation, have been verified as conforming to requirements. As set

out in paragraph 61 of HTA Directions 003/2010, storage facilities must separate and distinguish tissues and cells that are held in quarantine from those that are released and those that are rejected. Where necessary there must be separate storage provisions for tissues and cells collected in accordance with special criteria, such as positive donor serology. Quarantine storage can be achieved by the use of separate liquid nitrogen storage vessels. Where this would involve the transfer of donations from one storage vessel to another, it is appropriate to carry out a risk assessment of the procedure. Establishments may consider the use of hermetically-sealed double bags, or the over-wrapping of samples prior to storage, in order to improve the segregation of quarantine samples.

63. Paragraph 133 of HTA Directions 003/2010 sets out that a maximum storage time for tissues and cells must be specified. Where tissues and cells can be stored under different conditions and temperatures, expiry dates may need to take into account the different storage conditions. In the case of umbilical cord blood donations, data are not currently available to justify a requirement to discard samples on the basis of a specific period of storage in liquid nitrogen tanks. It may be appropriate to review the possible deterioration in quality of the tissues and cells when the expiry date is reached and assign a later expiry date based on the viability of the cells and a risk assessment of their use following prolonged storage, rather than discard the material. Establishments should maintain vigilance with regard to the storage of tissues and cells.

64. Similarly, it is difficult to define the minimum volume of cells or the minimum cell count in a donation which should be stored, as this may differ between establishments, depending on the method of collection and processing. Establishments should discuss the suitability for storage of low volume collections with parents, particularly where there is a requirement for a minimum volume due to processing methodology.

65. As set out in paragraphs 211-214 of HTA Directions 003/2010, establishments must have agreements and procedures in place to ensure that, in the event of termination of activities for whatever reason (including closure of the establishment or a third party establishment), stored tissues and cells, together with relevant records, are transferred to another HTA-licensed establishment.

Import and export

66. For the purposes of this guidance document, the terms 'import' and 'export' relate to the transportation of tissues and cells into or out of the

UK from any country which is not a member state of the EEA. Under this definition, import and export to countries which are not EEA states is a licensable activity, and can only be undertaken by establishments licensed for import and export by the HTA.

67. The EEA member states for these purposes are set out in HTA Directions 003/2010 and consist of the following countries:

Austria	Greece	Netherlands
Belgium	Hungary	Norway
Bulgaria	Iceland	Poland
Cyprus	Ireland	Portugal
Czech Republic	Italy	Romania
Denmark	Latvia	Slovakia
Estonia	Lichtenstein	Slovenia
Finland	Lithuania	Spain
France	Luxembourg	Sweden
Germany	Malta	United Kingdom
Gibraltar		

68. Import or export is not a licensable activity where it occurs between two licensed, accredited, designated or authorised establishments within the EEA and therefore a licence is not needed for import/export in those circumstances.

69. The movement of tissues and cells within the EEA is regarded as distribution and is covered in paragraphs 76-82 of this document under the heading 'Distribution'.

70. It should be noted that a licence is always needed for the distribution of imported material within the UK as this involves the distribution of stored tissues or cells to end users at some point, whether the material was stored in the UK or received from storage outside the UK. Distribution also includes the transport from the collection site to the establishment.

Requirements for moving tissues and cells into and out of the EEA

71. HTA Directions 003/2010 include specific provisions relating to the import of tissues and cells from countries which are not EEA member states. A licence for import is required for this activity. The tissues and cells must meet the requirements for quality and safety set out in paragraphs 203-210 of HTA Directions 003/2010.

72. Reference is made in HTA Directions 003/2010 to establishments satisfying themselves that the requirements for equivalent standards of quality and safety are achieved through contracts with suppliers of

tissues and cells which should outline relevant specifications and standard operating procedures. There should be systems in place to allow verification that these standards are being adhered to, including but not limited to site visits, audits and provision of written documentary evidence where appropriate.

73. HTA licensed establishments must comply with the HTA Code of Practice on Import/Export. In particular, establishments importing tissues or cells from countries which are not EEA member states should look for evidence to show that appropriate consent in relation to the eventual use of tissues or cells is part of the overall procurement process in the source country. The DI should also ensure that the establishment in the source country is meeting the standards set out in HTA Directions 003/2010 as they apply to procurement, donor documentation, processing, packaging labelling and transportation, traceability and requirements to report SAEs and SARs.

74. All of the biological tests set out in Annex B of HTA Directions 003/2010 **must** be carried out on all imported tissues and cells, regardless of whether they originate from inside or outside the EEA. In particular, testing for HTLV-1 antibody testing must be performed where appropriate. Donor testing is covered in more detail in paragraphs 43-54 of this document under the heading 'Testing'.

75. The DIs of umbilical cord blood establishments should ensure that procurement in countries outside the EEA is carried out by suitable personnel and that the name of the person responsible for the procurement is recorded; they should obtain an assurance that the individual procurer has received appropriate training and that this is documented. DIs should also assure themselves that consent is taken in accordance with local requirements and that suitable premises are used for the collection of umbilical cord blood.

Distribution

76. The transportation of tissues and cells into or out of the UK from countries which are not EEA member states is covered in more detail in paragraphs 66-75 of this document under the heading 'Import and Export'. The movement of tissues and cells within the UK is regarded as distribution and is covered in this section of the document.

77. Distribution includes the transportation and delivery of tissues or cells intended for treatment (human application). A person who, from any

premises, controls the provision of services for transporting tissues or cells is to be taken to distribute tissue or cells on those premises.

78. Organisations distributing tissues or cells from a procurement organisation to a tissue establishment must adhere to the general transport requirements outlined in paragraphs 152-154 of HTA Directions 003/2010. The requirements for the packaging and labelling of procured tissues and cells for transport are set out in paragraphs 114-115 of HTA Directions 003/2010.
79. The distribution of tissues and cells to end users within the UK is a licensable activity. The requirements for the distribution of tissues and cells, including arrangements for traceability, packaging and recall are set out in paragraphs 140-158 of HTA Directions 003/2010.
80. The requirements for the packaging and labelling of tissues and cells for transport to end users within the UK are set out in paragraphs 159-162 of HTA Directions 003/2010. When tissues are transported between licensed establishments, any agreement for that process must include provisions for maintaining traceability from donor to recipient and also the obligation to report SAEs and SARs. There should be an SLA in place between the establishments to detail their relative responsibilities in relation to transport, traceability, record keeping, reporting SAEs and SARs.
81. It is important that any agreement with an unlicensed third party undertaking distribution, or with any end user, includes an obligation on them to maintain traceability and to report SAEs and SARs to the DI at the HTA licensed establishment.
82. When distributing tissues or cells for end use the DI should ensure:
 - that risk assessments are in place for all aspects of the transport of tissues and cells
 - critical transport conditions such as temperatures and time limits are identified and maintained to preserve the quality and safety of tissues and cells
 - packaging and containers have been validated as being fit for purpose
 - if a third party is used to carry out distribution, the agreement with that party ensures that transport conditions are maintained

- the DI has the ability to initiate a recall of tissues or cells if required and appropriate processes and procedures are in place to do this and to document the actions taken
- the traceability of tissues and cells is maintained at all times
- the labelling of packaging and (if appropriate) shipping containers meets the standards set out in HTA Directions 003/2010

Third Party Agreements

83. A Third Party Agreement (TPA) enables an unlicensed organisation or person to carry out licensable activities on behalf of an HTA licensed establishment. The concept of third parties defined in this manner is not recognised in the EU Tissues and Cells Directives. It is a definition put in place by the Q&S Regulations to reduce the burden on HTA licensed establishments by increasing flexibility about arrangements for other persons and organisations to carry out activities on behalf of an establishment which is licensed by the HTA.

84. TPAs can be put in place for procurement, processing, testing, distribution, import or export – but not storage.

85. The establishment must itself be licensed for the activity which is to be carried out under a TPA. A TPA must also be put in place whenever a third party provides or supplies **goods or services that affect quality or safety of the tissues or cells**. An SLA is an appropriate alternative to a TPA for agreements between two organisations licensed by the HTA.

86. The requirements for a TPA are set out in paragraph 199 of HTA Directions 003/2010 and the DI should ensure that the relevant elements are captured in any TPA. The specific requirements for a TPA between a licensed umbilical cord blood establishment and a procurer are included in paragraph 199c of HTA Directions 003/2010. Annex E of HTA Directions 003/2010 provides a guidance template for TPAs.

87. A TPA should clearly set out the roles and responsibilities of each party in a manner that is easy to understand. For example:

- a. **Umbilical cord blood Company A** is responsible for:
 - donor selection
 - donor consent
 - provision of a collection kit

b. **Procurer B** is responsible for:

- risk assessment of procurement premises
- procurement of the umbilical cord blood in accordance with documented procedures and training
- procurement of a maternal blood sample for testing
- packaging and labelling of the collected samples

88. The responsibilities of the LH and DI relating to TPAs and SLAs are set down in the Q&S Regulations. Specifically, Regulation 12 of the Q&S Regulations states that it is a statutory duty of the DI to ensure that licensable activities carried out by third parties are subject to suitable practices and are carried out by suitable persons.

89. It is essential that establishments supervise the activities carried out on their behalf by third party organisations or individuals. It is important to note that the DI retains statutory responsibility for all activities carried out under the licence, including those under TPAs, and the DI therefore needs to be able to demonstrate that sufficient control measures are in place to ensure that the licensable activities are carried out by the third party in accordance with HTA licensing standards and HTA Directions 003/2010. In the case of processing, this will always include regular full audits of the entire service carried out independently by the DI at least at two yearly intervals. Additional measures which the DI can put in place to obtain assurance of suitable practices include:

- clear descriptions in the third party agreements of roles and responsibilities
- regular audit of third parties and relevant third party premises
- risk assessment of third parties and third party premises, including the identification of risks to the donor, recipient and staff
- if appropriate, attendance at external training sessions to assure the DI of the suitability of the training provided
- the provision of feedback, such as records showing samples which have been contaminated during any activity carried out by the third party. Such information can be used for trending and analysis by the third party to identify weaknesses or requirements for re-training

Procurement outside the licensing framework

90. Regulation 7 of the Q&S Regulations makes it clear that procurement must only be carried out under an HTA licence or in pursuance of a TPA. Procurement outside the HTA licensing framework is therefore a breach of the Q&S Regulations and is unlawful.

Umbilical cord tissue and other tissue types

91. A number of establishments which were originally licensed to procure and store umbilical cord blood have expressed an interest in expanding their activities to include work with other tissues, including umbilical cord tissue.

92. Standard condition 15 in Annex B of Human Application licences sets out that the DI must notify the HTA whenever the establishment proposes to procure, test, process, store, distribute, import or export a new type of tissue or cells, and where the processes required differ substantially from those previously employed. The new type of tissues or cells may not be procured, tested, processed, stored, distributed, imported or exported by the establishment until the HTA is satisfied that the establishment has suitable premises and employs suitable practices to carry out the proposed activity in respect of the new type of tissues or cells.

93. The HTA may require establishments to provide validation data which demonstrate that HTA standards are being met for each new tissue type. The data could include studies indicating that satisfactory numbers and types of viable cells are isolated during processing, and subsequently stored. In addition, the establishment might provide information confirming that environmental monitoring results are within the required range, and that the processing routinely achieves acceptably low levels of microbial contamination of the stored cells.

94. Some establishments store unprocessed umbilical cord tissue whereas others store mesenchymal stem cells derived from the tissue. Establishments should validate and risk assess their policies to provide assurance that the most appropriate procedures for processing and storage are undertaken. Parents must be fully informed of the differences between the storage of umbilical cord tissue and storage of stem cells derived from the tissue. The reasons for the choice of material for storage should be explained when consent for the process is obtained.

95. The processing of umbilical cord tissue to prepare mesenchymal stem cells could represent the manufacture of an advanced therapy medicinal

product (ATMP) as defined in European Commission Regulation EC 1394/2007. In general, if 'substantial manipulation', which includes the expansion of the cells, is carried out, the material produced is usually regarded as an ATMP. Establishments should seek advice from the Medicines and Healthcare products Regulatory Agency (MHRA) on the regulatory classification of the materials produced and a determination of whether these come into the category of ATMPs. If a product is classified as an ATMP, a manufacturing authorisation from the MHRA will be required.

Appendix 1 – Links to other relevant websites

- **HTA Website**
[HTA - The Human Tissue Authority](#)
- **HTA Directions 003/2010**
[HTA legal Directions](#)
- **HTA Licensing Standards**
http://www.hta.gov.uk/db/documents/HTA_Human_Application_v2.pdf
- **HTA Code of Practice 1: Consent**
[Code 1 -Consent](#)
- **HTA Code of Practice 8: Import and Export**
[Code 8 -Import and export](#)
- **Cord Blood FAQs**
[Cord blood procurement FAQs](#)
[Cord blood collection FAQs for parents](#)
- **Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment**
[http://www.hta.gov.uk/db/documents/Annex -
_Guide to Quality and Safety Assurance for Tissues and Cells for
Patient Treatment.pdf](http://www.hta.gov.uk/db/documents/Annex-_Guide_to_Quality_and_Safety_Assurance_for_Tissues_and_Cells_for_Patient_Treatment.pdf)
 - **Annex E to the Guide provides a guidance template for TPAs**
- **Eurocet website for Competent Authorities**
[Istituto Superiore di Sanità: Eurocet: Competent Authorities: List of Competent Authorities ...](#)
- **Other useful websites**
 - [Royal College of Obstetricians and Gynaecologists](#)
 - [Royal College of Midwives](#)

Glossary & Definitions

Terms used in this document have the same meaning as set out in the HTA's Codes of Practice and the Directives, unless otherwise stated.

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

ATMP, Advanced therapy medicinal product: This term means any of the following medicinal products for human use:

- a. a gene therapy medicinal product as defined in Part IV of Annex I to European Commission Directive 2001/83/EC,
- b. a somatic cell therapy medicinal product as defined in Part IV of Annex I to European Commission Directive 2001/83/EC, or
- c. a tissue engineered product as defined in point (b) of European Commission Regulation EC 1394/2007

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

This guide does not use this definition autologous graft given in the EU Directives which refers specifically to tissue removed and re-applied in the same procedure (direct use) and not at a later time.

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

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

Cells: Individual human cells or a collection of human cells when not bound by any form of connective tissue, including cell lines grown outside the human body but not including: Gametes; Blood and blood components.

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

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

Distribution: Transportation and delivery of tissues or cells intended for treatment (human application). 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 from those premises.

Donation: Donating human tissues or cells intended for treatment ((human application).

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

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

Export: Export from the United Kingdom to a place outside the United Kingdom.

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

HT Act: The Human Tissue Act 2004.

Human Application: In relation to tissue or cells, means use on or in a human recipient, including use in extracorporeal applications. It excludes the use of an autologous graft within the same surgical procedure.

Import: Import into the United Kingdom from a place outside the United Kingdom.

LH: Licence Holder, means a person who holds a licence under Schedule 1 of the Q&S Regulations.

Premises: Location where licensable activities are carried out.

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

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

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

Processing: All operations involved in the preparation, manipulation, preservation and packaging of tissues or cells intended for treatment (human application).

Q&S Regulations: Used throughout to refer to the Human Tissue (Quality and Safety for Human Application) Regulations 2007

Quarantine: 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, SAE: Any untoward occurrence which may be associated with the procurement, testing, processing, storage or distribution of tissue or cells intended for treatment (human application) and which, in relation to a donor of tissue or cells intended for treatment (human application) or a recipient of tissue or cells:

- a. might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions, or
- b. might result in, or prolong, hospitalisation or morbidity.

Serious adverse reaction, SAR: An unintended response, including a communicable disease, in a donor of tissue or cells intended for treatment (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.

SLA: Service level agreement.

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

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

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

Testing: The testing of blood samples from donors of tissues and cells for serological disease markers. In the context of this document, testing does not refer to microbiological testing, environmental monitoring or the testing or validation of equipment.

Third Party: A person with whom a LH, or the DI on behalf of the LH, has a third party agreement.

Third Party Agreement, TPA: An agreement in writing between a LH, or the DI on behalf of the LH, and another person which is made for the purpose of securing compliance with specified requirements of the Q&S 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.

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

- a. on which a third party procures, tests, processes or distributes, or 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: All constituent parts of the human body formed by cells, but does not include:

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

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

Validation (or '**qualification**' in the case of equipment or environments):

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

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