HTA
Human Tissue Authority

The HTA Compliance Resource for US Imports:

A guide to meeting UK regulatory requirements when tissues and cells for human application are imported from the United States of America

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Joint statement from HTA, FDA and AATB

The Human Tissue Authority, with technical assistance from the US Food and Drug Administration (FDA) and the American Association of Tissue Banks (AATB), supports this work and on-going collaboration to maintain the continued international exchange of safe human tissues and cells for human application.

Introduction

The HTA is the UK Competent Authority for the purposes of the EU Tissues and Cells Directives, which set standards of quality and safety in relation to human tissues and cells intended for human application. Establishments wishing to import human tissues and cells for human application from a country outside of the EU into the UK must be licensed by the HTA for the activity of import.

Importing tissue establishments must ensure that imports from third countries meet standards of quality and safety equivalent to those in the UK. The majority of imports originate in the US and we have identified a number of key differences in regulatory requirements. We have prepared this resource, with technical assistance from the FDA and AATB, to help UK-based importing tissues establishments (UK-ITEs) and US-based third country suppliers (US-3CSs) demonstrate with confidence that UK regulatory requirements have been met for human tissues and cells imported into the UK from the US for human application.

This resource explains the applicable UK regulatory requirements that differ from US requirements for human tissues and cells for human application[1], referencing the relevant legislation and regulations for each and suggesting actions that UK-ITEs and US-3CSs can take to meet the requirements.

[1]FDA requirements within sections of this document relating to donor infectious disease testing are applicable to human cells, tissues and cellular and tissue-based products (commonly referred to the in the US as 'HCT/Ps') regulated under Section 361 of the US Public Health Service Act or as drugs, devices, and/or biological products under the Federal Food, Drug, and Cosmetic Act and/or section 351 of the Public Health Service Act. FDA requirements within other sections of this guidance apply only to HCT/Ps regulated solely under Section 361 of the US Public Health Service Act, and this is explained within the relevant sections.

Contents

Applicable tissue and cell types[1]

The HTA regulates all of the tissue and cell types listed in the table below under the same legislation. The HTA requirements described in this tool apply to all of the tissue and cell types listed in the table below, whether for autologous or allogeneic use.

If you are interested in importing into the UK a tissue / cell type not listed here, or if you are unsure of how to classify your tissue / cell type of interest, then please contact the HTA directly.

Tissue type[2]	**HTA category**
Acellular bone chips	Skeletal tissues
Adipose tissue (e.g. adipocytes)	Other tissues or cells
Amniotic membrane	Other tissues or cells
Bone	Skeletal tissues
Bone marrow – minimally manipulated[3]	Blood cells and stem cells
Bone marrow – cryopreserved	Blood cells and stem cells
Bone marrow – related	Blood cells and stem cells
Bone marrow – unrelated	Blood cells and stem cells
Bone-suture-tendon allografts	Skeletal tissues
Cartilage/chondral tissue	Skeletal tissues
Cells for donor lymphocyte infusions – related	Blood cells and stem cells
Cells for donor lymphocytes infusions – unrelated	Blood cells and stem cells
Cornea	Ocular tissues
Corneal lenticules	Ocular tissues
Cryopreserved micronized skin	Skin
Decellularised nerve	Other tissues or cells
Decellularised skin	Skin
Demineralised bone	Skeletal tissues
Demineralised bone matrix + carrier	Skeletal tissues
Fibroblast and/or keratinocyte cells	Skin
Heart valves	Vascular tissues
Hepatocytes	Other tissues or cells
Human embryonic stem cells	Blood cells and stem cells
Iliac vessels	Vascular tissues
Limbal stem cells	Ocular tissues
Other blood cells	Blood cells and stem cells
Other ocular tissues	Ocular tissues
Other tissues or cells	Other tissues or cells
Other vessels	Vascular tissues
Ovarian and testicular tissues	Other tissues or cells
Pancreatic islets	Other tissues or cells
Peripheral blood stem cells – related	Blood cells and stem cells
Peripheral blood stem cells – unrelated	Blood cells and stem cells

(Table continues on following page)

Sclera	Ocular tissues
Tendons/ligaments	Skeletal tissues
Umbilical cord blood – related	Blood cells and stem cells
Umbilical cord blood – unrelated	Blood cells and stem cells
Umbilical cord tissue	Blood cells and stem cells
Whole skin	Skin

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[2]The FDA does not require donor testing for autologous donations; therefore, although HTA requirements for donor testing listed in this tool are applicable to tissues and cells for autologous use, FDA requirements listed are not.
[3] Donations of minimally manipulated bone marrow must still meet HTA requirements, but fall outside the FDA's regulatory remit (21CFR1271.3(d)(4)). For information on regulation of minimally manipulated bone marrow in the United States, please refer to the US Department of Health and Human Services Health Resources and Services Administration HRSA: http://bloodcell.transplant.hrsa.gov/.

Mandatory donor testing

UK requirements for mandatory donor testing are identical to those laid down in Annex II of the European Tissues and Cells Directive 2006/17/EC. A link to this legislation can be found in Appendix A. All EU Member States must adhere to these requirements. Some Member States also have additional national requirements, but this is not the case for the UK.

Required assays for mandatory donor testing

	UK HTA	US
Explanation	Immunological donor testing assays must be performed for HIV-1, HIV-2, Hepatitis B virus, Hepatitis C virus, and Treponema pallidum.	**FDA** FDA requires immunological testing for HIV-1, HIV-2, Hepatitis B virus, Hepatitis C virus and Treponema pallidum. For HIV and HCV, use of NAT assays is specified in guidance, in addition to immunological testing.
		AATB AATB standards specify that accredited organisations must perform immunological tests equivalent to those required in the UK and also requires NAT for HIV-1 and HCV. D4.354
Legislation/ Regulation	Commission Directive 2006/17/EC Annex II paragraph 1	21CFR1271.85(a) Section VI, 2007 FDA HCT/P donor testing guidance

	UK ITE	US 3CS
Action	Audit US supplier's donor testing processes to ensure that the assays used for mandatory donor testing are equivalent to UK requirements.	Provide evidence to the UK ITE that equivalent donor testing is performed. Equivalence is expected for AATB accredited organisations.

Validated tests for mandatory donor testing

	UK HTA Requirement	US Requirement
Explanation	Mandatory donor testing must be carried out using tests that have been validated for the purpose in accordance with current scientific knowledge, and CE marked, where appropriate.	**FDA** Required donor testing must be carried out using appropriate FDA-licensed, approved or cleared donor screening tests in accordance with the manufacturer's instructions.
		AATB Equivalent to FDA. D4.353
Legislation/ Regulation	Commission Directive 2006/17/EC Annex II paragraph 2.1	21CFR1271.80(c)

	UK ITE	US 3CS
Action	Audit US supplier's donor testing processes to ensure that only tests that have been FDA-licensed, approved or cleared are used, or in the case of HTLV-I, that tests are appropriately validated for the purpose in accordance with current scientific knowledge.	Provide evidence to the UK ITE that only tests that have been FDA licensed, approved or cleared are used, or in the case of HTLV-I, that tests are appropriately validated for the purpose in accordance with current scientific knowledge.

180-day repeat testing for living donors

	UK HTA Requirement	US Requirement
Explanation	**When repeat testing is required:** Mandatory donor testing must be repeated with a blood sample taken 180 days post donation for living donors where donated material is stored for long periods (>180-days before use). See below for exceptions. **When repeat testing is not required:** • Where donated material cannot be stored for long periods • When NAT is used in addition to immunological testing for HIV-1, HIV-2, HBV and HCV (and HTLV-1 where relevant) • Where processing of donated material includes a viral inactivation step validated for all viruses concerned • Donors of bone marrow and peripheral blood stem cells need only be screened on the donation sample using immunological methods even though material may be stored for longer.	**FDA** 180-day repeat testing of living donors is not required by FDA. FDA requires immunological testing for HIV-1, HIV-2, Hepatitis B virus, Hepatitis C virus, and Treponema pallidum. Use of NAT assays for HIV-1 and HCV is specified in guidance, in addition to immunological testing. **AATB** Equivalent to FDA. D4.354
Legislation/ Regulation	Commission Directive 2006/17/EC Annex II paragraph 2.5-2.6; HTA Directions 003/2010	21CFR1271.80 Section VI, 2007 FDA HCT/P donor testing guidance

	UK ITE	US 3CS
Action	Audit US supplier's donor testing processes to ensure that repeat or NAT testing is carried out for HIV-2, HBV (and HTLV-1 where relevant).	Provide evidence to the UK ITE that repeat or NAT testing requirements for living donors are met.

Mandatory donor testing: HTLV-I

	UK HTA Requirement	US Requirement
Explanation	HTLV-I immunological testing must be performed for donors who have had specific forms of contact with areas of high HTLV-I prevalence, including donors living in, or originating from, high-prevalence areas or with sexual partners originating from those areas or where the donor's parents originate from those areas. HTLV-I high prevalence areas defined by the European Centre for Disease Prevention and Control should be used to guide donor screening. As an alternative to screening donors for contact with HTLV-1 high prevalence areas, establishments may choose to test all donors for HTLV-1.	**FDA** HTLV-I testing is required only for donors of viable leukocyte-rich cells or tissue. **AATB** Equivalent to FDA. AATB standards note that HTLV testing may be required by foreign law. D4.354
Legislation/ Regulation	Commission Directive 2006/17/EC Annex II paragraph 1.2 Commission Directive 2012/39/EU	21CFR1271.85(b)(1)

	UK ITE	US 3CS
Action	Audit US supplier's donor testing processes to ensure that donors who have had the specified forms of contact with areas of high HTLV-I prevalence are tested appropriately for HTLV-I.	Provide evidence to the UK ITE that donors who have had the specified forms of contact with areas of high HTLV prevalence are tested appropriately for HTLV-I.

Specimen collection for mandatory donor testing: Living donors

For bone marrow and peripheral blood stem cells (PBSC) donors:

	UK HTA Requirement	US Requirement
Explanation	*'In the case of bone marrow and peripheral blood stem-cell collection, blood samples must be taken for testing within 30 days prior to donation.'*	**FDA** For donors of peripheral blood stem cells or bone marrow* the donor specimen for testing may be collected up to 30 days before recovery.
		AATB AATB does not include bone marrow and PBSCs in its accreditation programme.
Legislation/ Regulation	Commission Directive 2006/17/EC Annex II paragraph 2.7	21CFR1271.80(b)

	UK ITE	US 3CS
Action	No action required. FDA and HTA requirements are equivalent.	No action required. FDA and HTA requirements are equivalent.

**Minimally manipulated bone marrow for homologous use must still meet HTA requirements but falls outside the FDA's regulatory remit (21CFR1271.3(d)(4)). For information on regulation of this material in the United States, please refer to the US Department of Health and Human Services Health Resources and Services Administration HRSA: http://bloodcell.transplant.hrsa.gov/.*

For allogeneic living donors of tissues and cells other than peripheral blood stem cells or bone marrow):

	UK HTA Requirement	US Requirement
Explanation	*If 180-day repeat testing is performed:* Donor samples can be taken up to 30 days prior to or up to seven days post donation. Or *If 180-day repeat testing is not performed:* Donor samples must be obtained at the time of donation or, if not possible, within seven days post-donation; and, must be additionally tested using NAT.	**FDA** Donor specimens for testing must be collected at the time of recovery, or up to 7 days before or after recovery. **AATB** Equivalent to FDA. D4.351
Legislation/ Regulation	Commission Directive 2006/17/EC Annex II paragraph 2.5	21CFR1271.80(b)

	UK ITE	US 3CS
Action	Audit US supplier's donor testing processes to ensure the timing of donor testing sample recovery is appropriate in line with the information outlined above.	Provide evidence to the UK ITE that the timing of donor testing sample recovery is appropriate.

Specimen collection for mandatory donor testing: Deceased donors

	UK HTA Requirement	US Requirement
Explanation	Specimen for testing must be taken just prior to death or within 24hrs after death. The HTA interprets 'just prior to death' to mean usually within 24 hours prior to death and up to 7 days prior to death. If specimens for testing are taken >24 hours prior to death, then a documented rationale and risk assessment should be present. For the purposes of this guidance, the HTA considers that post-mortem blood samples should be collected as soon as possible after the donor's death and within 24 hours following circulatory arrest.	**FDA** Donor specimens for testing must be collected at the time of recovery, or up to 7 days before or after recovery. **AATB** Equivalent to FDA. D4.351
Legislation/ Regulation	Commission Directive 2006/17/EC Annex II paragraph 2.4	21CFR1271.80(b)

	UK ITE	US 3CS
Action	Audit US supplier's donor screening processes to ensure all blood samples for donor testing are taken just prior to death or no more than 24 hours after circulatory arrest. For specimens for donor testing taken >24 hours prior to death, the ITE should decide whether or not testing was performed appropriately based on the rationale and risk assessment provided by the 3CS.	Provide evidence to the UK ITE that all blood samples for donor testing are taken just prior to death or no more than 24 hours after circulatory arrest. If specimens for donor testing are taken >24 hours prior to death, then a documented rationale and risk assessment should be provided to the ITE.

Donor screening for malignant disease and diseases of unknown aetiology

	UK HTA Requirement	US Requirement
Explanation	Donation of most tissues and cells is contraindicated where there is a history or presence of malignant disease or of a disease of unknown aetiology. Screening of all donors for malignant disease and diseases of unknown aetiology is required.	**FDA** Screening of all donors for malignant disease and diseases of unknown aetiology is not specifically required.
		AATB Accredited organisations must screen for malignant disease, but screening for disease of unknown aetiology is not specifically required. D4.220; D4.310; D4.330; D4.340
Legislation/ Regulation	Commission Directive 2006/17/EC Annex I paragraph 1.1.3.	21CFR1271.75

	UK ITE	US 3CS
Action	Audit US supplier's donor screening processes to ensure all donors are screened for malignant disease and diseases of unknown aetiology according to EUTCD 2006/17/EC Annex I.	Provide evidence to the UK ITE that all donors are screened for malignant disease and diseases of unknown aetiology according to EUTCD 2006/17/EC Annex I.

Preparation process validation*

	UK HTA Requirement	US Requirement
Explanation	Validation of preparation processes affecting the quality and safety of donated tissues and cells must be documented. Authorisation of preparation processes by HTA's PPD Working Group is required prior to commencement of processing activity and prior to making significant changes to processing activities.**	**FDA** Where results of processing cannot be fully verified by subsequent inspections and tests, the process must be validated and approved according to established procedures. The validation activities and results must be documented. Authorisation by FDA of processing methods prior to beginning processing is not required.
		AATB Equivalent to FDA. AATB standards specify aspects of process that must be validated. E1.030 – E4.230
Legislation/ Regulation	Commission Directive 2006/86/EC; HTA Directions 003/2010	21CFR1271.220 - 230

	UK ITE	US 3CS
Action	Audit US supplier's validation of preparation processes and refer any concerns to the HTA.	Provide evidence to the UK ITE that preparation processes have been validated to produce the intended results.

** The FDA requirements listed in this section refer to HCT/Ps regulated solely under section 361 of the PHS Act only. For products regulated under section 351 or other US legislation/regulation, please contact the HTA directly to discuss regulatory requirements.*

*** The HTA defines a significant change as any change that may impact the quality and safety of the tissues / cells. UK-ITEs and US-3CSs who are unsure of whether or not to classify a processing change as 'significant' may* refer to HTA's guidance document or *contact the HTA directly.*

Traceability documentation*

	UK HTA Requirement	US Requirement
Explanation	***Raw data*** All records, including raw data, such as original temperature monitoring records, which are critical to the safety and quality of the tissues and cells, must be kept for at least 10 years after any expiry date, clinical use or disposal of the tissues and cells. ***Traceability data*** Data required for full traceability from donor to recipient must be kept for a minimum of 30 years following clinical use. In the event of termination of activities, the establishment must have in place agreements and procedures which ensure that full traceability data are maintained for a period of 30 years following end use or disposal.	**FDA** All records must be retained for 10 years after their creation, unless otherwise stated in the regulations. Records pertaining to particular HCT/Ps must be retained for at least 10 years after the date of its administration, or if unknown, then at least 10 years after the date of distribution, disposition or expiration, whichever is latest. **AATB** Equivalent to FDA. C1.300
Legislation/ Regulation	Directive 2004/23/EC Article 8 paragraph 4; HTA Directions 003/2010	21CFR1271.270(d)

	UK ITE	US 3CS
Action	Audit US supplier's data retention policy to ensure that the UK's more stringent requirements are met. The retention requirements should be outlined in the formal agreement.	Provide evidence to the UK ITE that the UK's more stringent data retention requirements are met.

** The FDA requirements listed in this section refer to HCT/Ps regulated solely under section 361 of the PHS Act only. For products regulated under section 351 or other US legislation/regulation, please contact the HTA directly to discuss regulatory requirements.*

Adverse event and reaction reporting*

	UK HTA Requirement	US Requirement
Explanation	Serious adverse events and reactions (SAEARs) refer to Serious Adverse Events (SAEs) and Serious Adverse Reactions (SARs); these are untoward events or unintended responses, respectively, that are related to the donated material and have the potential to adversely affect the patient(s). SAEARs must be reported to HTA within **24 hours** of discovery by the Designated Individual.	**FDA** Adverse reactions involving a communicable disease must be reported to FDA within **15 days** if fatal, life-threatening, results in permanent impairment of a body function or permanent damage to body structure, or necessitates medical or surgical intervention, including hospitalization. HCT/P deviations involving a distributed HCT/P and relating to core CGTP requirements must be reported to FDA within **45 days** of the discovery of the event.
		AATB AATB standards are silent on specific reporting timeframes. AATB accredited organisations must comply with FDA requirements. K4.100-300
Legislation/ Regulation	HTA Directions 003/2010	21CFR1271.350

	UK ITE	US 3CS
Action	Audit US supplier's adverse events reporting timeframes to ensure that UK's shorter timeframes are adhered to. SAEARs reporting responsibilities should be outlined in the formal agreement.	Provide evidence to the UK ITE that 3CS staff members are aware of the UK's SAEARs policy and thatsystems are in place to ensure that SAEARs (and suspected SAEARs) are reported to the ITE without delay and certainly within 24 hours of discovery.

** The FDA requirements listed in this section refer to HCT/Ps regulated solely under section 361 of the PHS Act only. For products regulated under section 351 or other US legislation/regulation, please contact the HTA directly to discuss regulatory requirements.*

Appendix A: Resources

Directive 2004/23/EC of the European Parliament and of the Council: the main piece of European legislation that sets standards for quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells; commonly referred to as the 'Parent Directive' or the 'Mother Directive'; http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1435743395263&uri=CELEX:32004L0023

Commission Directive 2006/17/EC: implements for Directive 2004/23/EC as regards certain technical requirements regarding the donation, procurement and testing of human tissues and cells for human application; commonly referred to as the 'first technical Directive'; http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1435743348718&uri=CELEX:32006L0017

Commission Directive 2006/86/EC: implements Directive 2004/23/EC as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells for human application; commonly referred to as the 'second technical Directive'; http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1435743270691&uri=CELEX:32006L0086

Commission Directive 2012/39/EU: amends Directive 2006/17/EC as regards certain technical requirements for the testing of human tissues and cells; http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32012L0039

Commission Directive (EU) 2015/566: implementing Directive 2004/23/EC as regards the procedures for verifying the equivalent standards of quality and safety of imported tissues and cells Text with EEA relevance; http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ:JOL_2015_093_R_0007

Human Tissue (Quality and Safety of Tissues and Cells for Human Application) Regulations 2007: the statutory instrument formally adopting Directive 2004/23/EC, the first technical Directive (2006/17/EC) and the second technical Directive (2006/86/EC) into UK law; commonly referred to as the 'Q&S Regulations'; https://www.hta.gov.uk/sites/default/files/Q&S_Human_Application_Regs_2007.pdf

European Centre for Disease Prevention and Control. Technical Report. Geographical distribution of areas with a high prevalence of HTLV-1 infection. http://ecdc.europa.eu/en/publications/Publications/geographical-distribution-areas-high-prevalence-HTLV1.pdf.

Standards for Tissue Banking. American Association of Tissue Banks. 13th Edition.

Title 21, Code of Federal Regulations, Part 1271, Human Cells, Tissues, and Cellular and Tissue-Based Products. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=1271

Guidance for Industry, Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), February 27, 2007. http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM091345.pdf

Appendix B: Key terms

CE-marked: an indication of a product's compliance with EU legislation; allows the free movement of products within the European market; by placing the CE marking on a product a manufacturer is declaring, on his sole responsibility, conformity with all of the legal requirements to achieve CE marking. (https://www.gov.uk/ce-marking).

Designated Individual (DI): a UK term referring to the 'Responsible Person' defined in Article 17 of Directive 2004/23/EC; the DI has the primary (legal) responsibility under Regulation 12 of the Q&S Regulations for ensuring regulatory compliance.

European Tissues and Cells Directives (EUTCD): refers to Directive 2004/23/EC and its implementing Directives.

HTA Directions 003/2010: consolidate and clarify the standards required under the Human Tissue (Quality and Safety of Tissues and Cells for Human Application) Regulations 2007 and are published as the *Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment.*

Human application: the use of tissues or cells on or in a human recipient and extracorporal applications (Directive 2004/23/EC).

Human cells, tissues, or cellular or tissue-based products (HCT/Ps): articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient (21CFR1271.3(d)).

Importing Tissue Establishment (ITE): 'a tissue bank or a unit of a hospital or another body established within the Union which is a party to a contractual agreement with a third country supplier for the import into the Union of tissues and cells coming from a third country intended for human application' (Commission Directive (EU) 2015/566).

Serious Adverse Events and Reactions (SAEARs): a term used to refer collectively to Serious Adverse Events (SAEs) and Serious Adverse Reactions (SAR).

Serious Adverse Event (SAE): 'any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity.' (Directive 2004/23/EC).

Serious Adverse Reaction (SAR): 'an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity.' (Directive 2004/23/EC).

Third Country Supplier (3CS): 'a tissue establishment or another body, established in a third country, which is responsible for the export to the Union of tissues and cells it supplies to an importing tissue establishment. A third country supplier may also carry out one or more of the activities, which take place outside of the Union, of donation, procurement, testing, processing, preservation, storage or distribution of tissues and cells imported into the Union.' (Commission Directive (EU) 2015/566).