Site visit inspection report on compliance with HTA licensing standards
Inspection date: **10-12 March 2020**

BioVault

HTA licensing number 11063

Licensed under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended)

and

Licensed under the Human Tissue Act 2004

Licensable activities carried out by the establishment

Licensed activities – Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended)

'E' = Establishment is licensed to carry out this activity and is currently carrying it out.

'TPA' = Third party agreement; the establishment is licensed for this activity but another establishment (not licensed by the HTA) carries out the activity on their behalf.

Site	Procurement	Processing	Testing	Storage	Distribution	Import	Export
BioVault	E	E	TPA	E	E	E	E

Tissue types authorised for licensed activities – Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended)

'Authorised' = Establishment is authorised to carry out this activity and is currently carrying it out.

'Authorised*' = Establishment is authorised to carry out this activity but is not currently carrying it out.

Tissue Category; Tissue Type	Procurement	Processing	Testing	Storage	Distribution	Import	Export
Progenitor Cell, Haematopoietic, Bone Marrow; Bone		Authorised*		Authorised*	Authorised*		

Marrow							
Progenitor Cell, Haematopoietic, PBSC; PBSC		Authorised		Authorised	Authorised		
Mature Cell, MNC; DLI		Authorised		Authorised	Authorised		
Progenitor Cell, Hematopoietic, Cord Blood; Cord Blood	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised
Umbilical Cord; Cord Tissue	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised	Authorised
Membrane, Fascia Lata; Fascia Lata				Authorised*	Authorised*	Authorised*	
Musculoskeletal, Bone; Bone				Authorised	Authorised	Authorised	
Musculoskeletal, Tendon & Ligament; Ligament				Authorised	Authorised	Authorised	
Musculoskeletal, Tendon & Ligament; Tendon				Authorised	Authorised	Authorised	
Musculoskeletal, Tendon & Ligament;				Authorised	Authorised	Authorised	

Menisci							

Licensed activities – Human Tissue Act 2004

'Licensed' = Establishment is licensed to carry out this activity and is currently carrying it out.

Area	Storage of relevant material which has come from a human body for use for a scheduled purpose
BioVault	Licensed

Summary of inspection findings

The HTA found the Designated Individual (DI) and the Licence Holder (LH) to be suitable in accordance with the requirements of the legislation.

Although the HTA found that BioVault (the establishment) had met the majority of the HTA's standards, four minor shortfalls were found against standards for Governance and Quality.

The HTA has assessed the establishment as suitable to be licensed for the activities specified, subject to corrective and preventative actions being implemented to meet the shortfalls identified during the inspection.

Compliance with HTA standards

Minor Shortfalls

Human Tissue (Quality and Safety for Human Application) Regulations 2007 Standards

Standard	Inspection findings	Level of shortfall
GQ1 All aspects of the establishment's work are supported by ratified documented policies and procedures as part of the overall governance process.		
n) The establishment ensures imports from non-EEA states meet the standards of quality and safety set out in Directions 002/2018.	Testing of donors is undertaken by a subcontractor (SC) of the establishment's third country supplier (3CS) for all imported tissue and cell products. The hepatitis B (HBV) testing kit, used by the SC, is not validated for use on blood samples from cadaveric donors. Furthermore, the establishment's 3CS that aseptically processes tissue products, did not meet the requisite air particle monitoring requirements at rest and in operation, as set out in Directions 002/18.	**Minor**

GQ4 There is a systematic and planned approach to the management of records.		
b) There is a system for the regular audit of records and their content to check for completeness, legibility and accuracy and to resolve any discrepancies found.	During the audit of the processing records, examples were identified where time and temperature deviations during the transit of umbilical cord blood (UCB) and tissue (UCT), were not been recorded as expected. The establishment's incoming checks and audits of the processing records are not sufficiently robust to identify these deviations.	**Minor**

GQ5 There are documented procedures for donor selection and exclusion, including donor criteria.		
a) Donors are selected either by the establishment or the third party acting on its behalf in accordance with the criteria required by Directions 002/2018.	The documented procedures for donor selection and exclusion do not screen for ingestion of, or exposure to, a substance (such as cyanide, mercury, gold) that may be transmitted to recipients in a dose that could endanger their health, as set out in Annex A of the Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient treatment. *Prior to the final report being issued the DI submitted evidence of the actions taken in relation to the above shortfall. The HTA has assessed this evidence as satisfactory and considers this standard to be met.*	**Minor**
b) The testing of donors by the establishment or a third party on behalf of the establishment is carried out in accordance with the requirements of Directions 003/2010.	Testing of UCB and UCT donors is carried out by a third party on behalf of the establishment. Since the previous inspection, the third party has undertaken validation work to demonstrate that the test kits are reliable when used to analyse blood samples that have been exposed to high temperatures during transit or that have had extended shipping times. The HTA has not been provided with evidence which confirms that the syphilis testing kits are suitable for use on such samples. Furthermore, the data submitted by the establishment suggests the validation work was performed on a single sample of blood. The establishment was unable to provide adequate assurance that a suitable sample size was used.	**Minor**

The HTA requires the DI to submit a completed corrective and preventative action (CAPA) plan setting out how the shortfalls will be addressed, within 14 days of receipt of the final report (refer to Appendix 2 for recommended timeframes within which to complete actions). The HTA will then inform the establishment of the evidence required to demonstrate that the actions agreed in the plan have been completed.

Advice

The HTA advises the DI to consider the following to further improve practice:

Number	Standard	Advice
1.	GQ1(h)	The DI is advised to update the procedure on product receipt to include the location of the quarantine area for cold and ambient temperature tissue products.
2.	GQ4(b)	On receipt of UCB and UCT samples, the time in transit is manually calculated. Samples that exceed the validated time in transit are not always flagged. The DI is advised to review the establishment's receipt procedures to identify ways to strengthen the systems for identifying non-conforming units. Given in-house IT expertise, the DI may wish to explore whether relevant checks can be automated.
3.	GQ6(d)	The establishment has introduced pre-release checks on the Single European Code (SEC) in response to identifying two instances where the SEC applied to tissue products was not in line with requirements. The DI is advised to ensure that these checks are reflected in relevant procedures.
4.	GQ7a	The establishment has procedures in place for the management of deviations, incidents and reporting of adverse events and reactions to the HTA. During the inspection, examples were seen where the establishment's procedure for logging incidents was not followed. This resulted in incidents not being logged or being logged at a later time. Examples of these included a customer complaint, temperature excursions of products in transit, and products exceeding the validated transit time.

		The DI is advised to consider including examples of deviations, reportable and non-reportable incidents as part of staff induction and ongoing training to ensure that all members of staff understand the process and what it involves.
5.	PFE2(c)	The DI is advised to continue with the plans to replace the contamination control mat located between the Grade D and C areas of the clean room. The DI should ensure all contamination control mats are maintained in accordance with the manufacturer's instructions to assure himself that they are effective.
6.	PFE5(f)	The DI is advised to review and update the cleaning and decontamination checklist to include the routine monitoring of the transfer hatch in the clean-room and the sterile welder used within the clean-room.

Background

BioVault (the establishment) has been licensed by the HTA since July 2006 under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended) and the Human Tissue Act (2004) (HT Act). The establishment is licensed for procurement, processing, storage, testing, distribution, import and export of umbilical cord blood (UCB) and cord tissue (UCT).

The establishment also provides a processing service for peripheral blood stem cells (PBSCs), bone marrow (BM) and peripheral blood lymphocytes for donor lymphocyte infusion (DLI), which have been procured under another establishment's HTA licence. PBSCs, BM and DLIs are processed by Biomedical Scientists from the second establishment under an agreement with BioVault. Until recently the establishment also processed PBSCs procured at a third HTA-licensed establishment, but this service is no longer taking place.

In addition to the activities above, BioVault imports bone, fascia lata, tendon, ligament and menisci products for allogeneic use from a third country supplier (3CS) for storage and distribution to end-users. The establishment is responsible for ensuring all imported material complies with all applicable HTA standards.

This was the seventh site visit inspection of the establishment; the most recent previous inspection took place in March 2018. Since the previous inspection, there have been no significant changes to the licence arrangements or the activities carried out under the licence.

Description of inspection activities undertaken

The HTA's regulatory requirements are set out in Appendix 1. The inspection team covered the following areas during the inspection:

Standards assessed against during inspection

There are 121 standards in the Human Application sector of which 115 were assessed. Standards GQ1f and PFE1d were not applicable and standards GQ3c, GQ3d, GQ3h and GQ3i were not assessed.

The establishment also stores relevant material for research under Research Ethics Committee (REC) approval, which is still in date. Therefore, storage of this material is exempted from the licensing requirements of the Act and compliance against these standards was not assessed.

Review of governance documentation

The inspection team undertook a review of documentation relevant to the establishment's licensable activities. This included procedural documents related to processing, import and distribution; records for maintenance of equipment; temperature monitoring records for the storage units including the liquid nitrogen tanks; agreements; minutes of governance meetings; incidents; audits; risk assessments and staff training records.

Visual inspection

The inspection included a visual inspection of the sample receipt, processing, cryostorage and ambient temperature storage areas. The inspection team observed processing activities conducted at the establishment including cord blood, cord tissue and DLI processing.

Audit of records

Representative records associated with each product were reviewed. These included:

- a detailed review of records relating to six UCB and four associated UCT samples received from six clients. Two of the clients were from the UK and four from overseas. These records included documents relating to consent; receipt and acceptance checks (*Advice item, GQ4(b)*); processing, including environmental monitoring; donor testing; storage; end-use; and disposal, where applicable. Additionally, the inspection

team reviewed two examples of letters sent to clients in instances where the UCB units did not meet the establishment's acceptance criteria. The location of two UCB and one UCT samples was cross-checked against the electronic records. No discrepancies were noted.

- the processing records of three autologous stem cell donors and a DLI donor that were procured at the two other HTA-licensed establishments. No discrepancies were noted.
- the processing records of four imported products selected prior to the inspection, including two bone products, one meniscus and one tendon. These records included documents relating to donor consent, mandatory serology and sterility testing, environmental monitoring or terminal sterilisation certificates, and certificates of donor eligibility, as appropriate. Discrepancies were noted during the review of the environmental monitoring records of two aseptically processed products *(Shortfall against standard GQ1(n)).*
- a traceability audit of two tendon products currently in -80°C storage and deemed suitable for release to end-users. These had been distributed from another establishment within the European Economic Area (EEA).
- a traceability audit of four imported bone products currently in storage at room temperature, cross-checked against the electronic records. The inspection team also reviewed the processes related to sample receipt and distribution, including the use of the Single European Code (SEC). Two of the imported tissue products currently in storage were labelled with the SEC soon after the implementation of the Coding Directive. The initial format of the SEC was not in line with the requirements. For example, the unique donation number included a dash within the 13 alphanumeric characters and the product identification sequence did not include the split number (*Advice item, GQ6(d)*). No other discrepancies were noted.

Meetings with establishment staff

Discussions were held with the DI who is also the Quality Manager for the establishment. Round table discussions were held with key staff involved with the processing of UCB and UCT, customer operations, audits, incident reporting, quality management systems and receipt, storage and distribution of imported tissue products. Round table discussions were also held with members of staff responsible for receipt and processing of PBSCs, DLI and BM.

Report sent to DI for factual accuracy: 2020.04.09

Report returned from DI: 2020.04.15

Final report issued: 2020.05.01

Completion of corrective and preventative actions (CAPA) plan

Based on information provided, the HTA is satisfied that the establishment has completed the agreed actions in the CAPA plan and in doing so has taken sufficient action to correct all shortfalls addressed in the Inspection Report.

Date: 7 February 2022

Appendix 1: The HTA's regulatory requirements

The HTA must assure itself that the DI, Licence Holder, premises and practices are suitable.

The statutory duties of the DI are set down in Section 18 of the Human Tissue Act 2004. They are to secure that:

- the other persons to whom the licence applies are suitable persons to participate in the carrying-on of the licensed activity;
- suitable practices are used in the course of carrying on that activity; and
- the conditions of the licence are complied with.

The HTA developed its licensing standards with input from its stakeholders. They are designed to ensure the safe and ethical use of human tissue and the dignified and respectful treatment of the deceased. The HTA inspects the establishments it licences against four groups of standards:

- consent
- governance and quality systems
- premises facilities and equipment
- disposal.

This is an exception-based report: only those standards that have been assessed as not met are included. Where the HTA determines that a standard is not met, the level of the shortfall is classified as 'Critical', 'Major' or 'Minor' (see Appendix 2: Classification of the level of shortfall). Where HTA standards are fully met, but the HTA has identified an area of practice that could be further improved, advice is given to the DI.

Reports of HTA inspections carried out from 1 November 2010 are published on the HTA's website.

Appendix 2: Classification of the level of shortfall (HA)

Where the HTA determines that a licensing standard is not met, the improvements required will be stated and the level of the shortfall will be classified as ‘Critical’, ‘Major’ or ‘Minor’. Where the HTA is not presented with evidence that an establishment meets the requirements of an expected standard, it works on the premise that a lack of evidence indicates a shortfall.

The action an establishment will be required to make following the identification of a shortfall is based on the HTA's assessment of risk of harm and/or a breach of the Human Tissue Act 2004 (HT Act), Human Tissue (Quality and Safety for Human Application) Regulations 2007, or associated Directions.

1. **Critical shortfall:**

   A shortfall which poses a significant direct risk of causing harm to a recipient patient or to a living donor,

   Or

   A shortfall which poses a significant risk to human safety and/or dignity or is a breach of the HT Act or associated Directions,

   Or

   A number of ‘major’ shortfalls, none of which are critical on its own, but viewed cumulatively represent a systemic failure and therefore are considered ‘critical’.

   A critical shortfall may result in one or more of the following:

   - A notice of proposal being issued to revoke the licence
   - Some or all of the licensable activity at the establishment ceasing with immediate effect until a corrective action plan is developed, agreed by the HTA and implemented.
   - A notice of suspension of licensable activities
   - Additional conditions being proposed
   - Directions being issued requiring specific action to be taken straightaway

2. Major shortfall:

A non-critical shortfall.

A shortfall in the carrying out of licensable activities which poses an indirect risk to the safety of a donor or a recipient

or

A shortfall in the establishment's quality and safety procedures which poses an indirect risk to the safety of a donor or a recipient;

or

A shortfall which indicates a major deviation from the Human Tissue (Quality and Safety for Human Application) Regulations 2007 or the HTA Directions;

or

A shortfall which indicates a breach in the relevant Codes of Practice, the HT Act and other relevant professional and statutory guidelines;

or

A shortfall which indicates a failure to carry out satisfactory procedures or a failure on the part of the designated individual to fulfil his or her legal duties;

or

A combination of several 'minor' shortfalls, none of which is major on its own, but which, viewed cumulatively, could constitute a major shortfall.

In response to a major shortfall, an establishment is expected to implement corrective and preventative actions within 1-2 months of the issue of the final inspection report. Major shortfalls pose a higher level of risk and therefore a shorter deadline is given, compared to minor shortfalls, to ensure the level of risk is reduced in an appropriate timeframe.

3. Minor shortfall:

A shortfall which cannot be classified as either critical or major and, which can be addressed by further development by the establishment.

This category of shortfall requires the development of a corrective action plan, the results of which will usually be assessed by the HTA either by desk-based review or at the time of the next inspection.

In response to a minor shortfall, an establishment is expected to implement corrective and preventative actions within 3-4 months of the issue of the final inspection report.

Follow up actions

A template corrective and preventative action plan will be sent as a separate Word document with the final inspection report. Establishments must complete this template and return it to the HTA within 14 days of the issue of the final report.

Based on the level of the shortfall, the HTA will consider the most suitable type of follow-up of the completion of the corrective and preventative action plan. This may include a combination of

- a follow-up site-visit inspection
- a request for information that shows completion of actions
- monitoring of the action plan completion
- follow up at next routine site-visit inspection.

After an assessment of the proposed action plan establishments will be notified of the follow-up approach the HTA will take.