Site visit inspection report on compliance with HTA licensing standards
Inspection date: **27-28 November 2019**

Birmingham Children's Hospital
HTA licensing number 11005

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.
'SLA' = Service level agreement; the establishment is licensed for this activity but another establishment (licensed) carries out the activity on their behalf.

Site	Procurement	Processing	Testing	Storage	Distribution	Import	Export
Birmingham Children's Hospital	E	E	SLA	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.
'SLA' = Service level agreement; the establishment is licensed for this activity but another establishment (licensed) carries out the activity on their behalf.

Tissue Category; Tissue Type	Procurement	Processing	Testing	Storage	Distribution	Import	Export
Cardiovascular, Valves; Heart Valves	Authorised*	Authorised	SLA	Authorised	Authorised		
Cardiovascular, Valves; Pulmonary Patches	Authorised*	Authorised	SLA	Authorised	Authorised		
Cardiovascular, Vessels; Conduits	Authorised*	Authorised	SLA	Authorised	Authorised		
Cardiovascular, Vessels; Other Vessels				Authorised			
Progenitor Cell, Haematopoietic, Bone Marrow; Bone Marrow	Authorised	SLA	SLA	SLA	SLA		
Progenitor Cell, Haematopoietic, PBSC; PBSC	Authorised	SLA	SLA	SLA	SLA		
Mature Cell, MNC; DLI	Authorised	SLA	SLA	SLA	SLA		
Membrane, Amniotic; Amniotic Membrane				Authorised			

Musculoskeletal, Bone; Bone			Authorised*	Authorised			
Musculoskeletal, Bone; Bone Struts				Authorised			
Musculoskeletal, Bone; Cranial Flaps				Authorised			
Ocular, Corneas; Cornea				Authorised			
Ocular, Sclera; Sclera				Authorised			
Skin; Skin	Authorised			Authorised	Authorised		

Licensed activities – Human Tissue Act 2004

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

Area	Storage of relevant material which has come from a human body for use for a scheduled purpose
Birmingham Children's Hospital	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 Birmingham Children's Hospital (the establishment) had met the majority of the HTA's standards, 13 minor shortfalls were found against standards for Governance and Quality, and Premises, Facilities and Equipment. These related to the content

of controlled procedures and records, the scope of the establishment's internal audits, the lack of an independent audit in the last two years, retention of raw data, the scope of the establishment's donor exclusion criteria, incomplete traceability records and the lack of procedures and records implementing the requirements of the Single European Code (SEC), insufficient systems for documenting incidents, maintenance and monitoring of the cleanroom environment and the suitability of temperature monitoring systems and oversight.

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

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

Minor Shortfalls

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.		
b) There are procedures for all licensable activities that ensure integrity of tissue and / or cells and minimise the risk of contamination.	During the inspection examples were identified where the establishment's standard operating procedures (SOPs) did not accurately reflect current practices: • there was an active SOP in theatres for the snap freezing of cranial flaps, which is not aligned with current heart valve bank (HVB) practice. The suitability of SOPs related to this procedure was a finding at the last inspection; and • the SOP describing the processing of heart valves, conduits and patches does not provide sufficient detail to guide processing staff	**Minor**

	through each stage of the processing pathway. It also does not provide sufficient guidance at key decision-making points, such as assessing the quality of the valves to determine whether whole valves, patches or conduits should be prepared from the donated tissue. HVB staff reported that images of processed tissue are taken and stored with the processing records; this requirement is not included in the SOP.	
g) There are procedures to ensure that an authorised person verifies that tissues and / or cells received by the establishment meet required specifications.	The establishment's SOPs do not set out the checks to be undertaken when receiving tissue purchased from other HTA-licensed establishments. In addition, establishment records do not capture all the checks undertaken by staff prior to accepting heart tissue for processing.	**Minor**
GQ2 There is a documented system of quality management and audit.		
b) There is an internal audit system for all licensable activities.	The establishment does not undertake documented audits of temperature monitoring records associated with HVB and stem cell transplant (SCT) activities. During the inspection, examples were noted of incomplete records and excursions from specified temperature ranges that had not been reviewed or commented upon.	**Minor**
c) An audit is conducted in an independent manner at least every two years to verify compliance with protocols and HTA standards, and any findings and corrective actions are documented.	The establishment has not undertaken an independent audit against relevant HTA licensing standards in the last two years.	**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. j) Records are kept of products and material coming into contact with the tissues and / or cells.	The establishment does not have systems in place for the regular audit of bone marrow procurement records. During the inspection, an example was identified in which a form used to record details of a bone marrow procurement within the theatre had not been fully completed. As a result, key information related to this event, including details of the products and materials coming into contact with the procured cells, was not available within the establishment's records.	**Minor**
h) Raw data which are critical to the safety and quality of tissues and cells are kept for 10 years after the use, expiry date or disposal of tissues and / or cells.	Storage equipment related to HVB activities is monitored using a commercially available wireless temperature monitoring system. The Trust has an agreement with the manufacturer which sets out the manufacturer's responsibilities regarding the storage of raw data. The agreement requires the manufacturer to retain raw data for 'up to 30 years' and does not specify a minimum retention period. Therefore, the agreement does not ensure that temperature monitoring data will be retained for 10 years after the use, expiry date or disposal of stored tissue.	**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.	Donor selection procedures for donated hearts do not include all of the mandatory exclusion criteria required by Directions 002/2018. SCT controlled forms used to assess donor suitability against a range of acceptance and exclusion criteria do not explicitly set out the mandatory exclusion criteria related to prion diseases, xenografts, poisons and heavy	**Minor**

	metals.	
GQ6 A coding and records system facilitates traceability of bodies, body parts, tissues and cells, ensuring a robust audit trail.		
b) An audit trail is maintained, which includes details of when the tissues and / or cells were acquired and from where, the uses to which the tissues and / or cells were put, when the tissues and / or cells were transferred elsewhere and to whom.	The establishment maintains a series of databases to track the receipt, storage and use of tissues purchased from other HTA-licensed establishments. SOPs state that traceability information is also recorded in patient clinical notes and theatre care plans. During a review of traceability records, several instances were identified where details of purchased tissues had not been recorded within the recipient's clinical notes. In some of these cases it could not be determined if the tissue released from the HVB for a planned procedure had been required, or, if not required, had been sensitively disposed of.	**Minor**
c) The establishment has procedures to ensure that tissues and / or cells imported, procured, processed, stored, distributed and exported are traceable from donor to recipient and vice versa.		
d) The requirements of the Single European Code are adhered to as set out in Directions 002/2018.	There are no documented procedures describing how the establishment meets the requirements of the SEC for tissue purchased and stored for end-use. Several examples were identified in which the SEC had not been retained in traceability records following use in patient treatment.	**Minor**
GQ7 There are systems to ensure that all adverse events are investigated promptly.		
a) There are procedures for the identification, reporting, investigation and recording of adverse events and	The establishment's procedures set out that clinical incidents related to the SCT service are captured within the hospital's clinical incident reporting system. However, this system was not routinely used to capture records of serious adverse events and reactions (SAEARs) reported to the HTA, or to	**Minor**

reactions, including documentation of any corrective or preventative actions.	register incidents such as positive microbiology reports received from donor registries that supply cells for transplantation. There is also no formal system in place to document timelines, corrective and preventative actions (CAPAs) and responsibilities for non-clinical incidents that have the potential to impact on the quality and safety of SCT cell products.	
PFE2 Environmental controls are in place to avoid potential contamination.		
b) Where processing of tissues and / or cells involves exposure to the environment, it occurs in an appropriate, monitored environment as required by Directions 002/2018.	The establishment's particle monitor was sent off-site for re-calibration. During the period in which the counter was not available, three processing events took place. The establishment did not make alternative arrangements to ensure that processing took place in an appropriately monitored environment. There was no documented rationale, risk assessment or concessionary release process undertaken for the tissues associated with these three processing events. Related to this, the heart valve processing record does not prompt establishment staff to record key information such as the time at which particle monitoring is started and stopped. As a result, records of processing do not demonstrate that particle monitoring took place throughout the period in which the tissue was exposed to the environment. In addition, the establishment was not able to provide a documented procedure setting out the incubation strategy for the tryptic soy agar (TSA) plates used in routine environmental monitoring, sessional monitoring and operator finger dabs.	**Minor**

PFE3 There are appropriate facilities for the storage of bodies, body parts, tissues, cells, consumables and records.		
a) Tissues, cells, consumables and records are stored in secure environments and precautions are taken to minimise risk of damage, theft or contamination.	The establishment monitors the temperature of storage areas, fridges and freezers using either a wireless monitoring system or stand-alone thermometers. Several issues were identified in relation to the monitoring undertaken using the stand-alone thermometers: • the thermometers were labelled as calibrated by the manufacturer, but establishment staff were not able to produce the associated calibration certificates; • the thermometers had the capability to provide continuous temperature monitoring through the use of the inbuilt maximum-minimum temperature logging function. However, these maximum and minimum temperature measurements were not being recorded. Instead, staff recorded the temperature displayed at the time of the check (i.e. a 'spot-check'); • a review of temperature monitoring records identified several examples where daily temperature checks had not been undertaken. Checks also did not take place during the weekend; and • several examples were identified where the temperature in a room used to store heparin for bone marrow procurement had exceeded the heparin manufacturer's specified temperature range. These excursions were not commented on or communicated to the establishment staff for assessment. Taken together, these findings do not provide sufficient assurance that critical reagents are stored in appropriately monitored environments and that excursions from the manufacturer's specified temperature ranges will be	**Minor**

	detected, reported and assessed by trained establishment personnel.	
PFE5 Equipment is appropriate for use, maintained, quality assured, validated and where appropriate monitored.		
a) Critical equipment and technical devices are identified, validated, regularly inspected and records are maintained.	The establishment was not able to provide documentation or schedules relating to the routine maintenance of cleanroom high-efficiency particulate air (HEPA) filters.	**Minor**
b) Critical equipment is maintained and serviced in accordance with the manufacturer's instructions.		

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.	General	At present, the establishment does not release vessels procured under the Quality and Safety of Organs Intended for Transplantation Regulations 2012 for human application under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended) but is considering the feasibility of undertaking this activity. The DI is advised of the requirement to contact the HTA prior to commencing this activity, to ensure the necessary

		authorisations are in place. The DI is further advised of the requirement to inform the HTA before undertaking the storage of any new tissue types, such as new types of tissues that may be purchased for end-use.
2.	GQ1b	Serology and microbiology samples may be stored at 2-8°C within the HVB before being sent to the relevant laboratories for testing. The DI is advised to define the maximum time that serology and microbiology samples can be stored at 2-8°C prior to testing within the establishment's procedures, to help ensure that the validated parameters of the tests being undertaken are not exceeded.
3.	GQ1c	Although the establishment is undertaking governance meetings, there are times when meetings related to the SCT service may be delayed or cancelled due to staff availability. The DI is advised to ensure that governance meetings occur at the frequency defined within establishment procedures, to support the timely sharing of information and follow up of open actions related to activities under the licence.
4.	GQ1j	During the inspection, a needle pack which had passed the manufacturer's expiry date was found in a pre-prepared bone marrow collection kit. The DI is advised to introduce a procedure whereby there is a documented check of kit components immediately prior to the kit being supplied to theatres for use. The use of such a system may help to ensure that all collection kit components are present, undamaged, and within the manufacturer's expiry date.
5.	GQ4h	The establishment uses a controlled form to record checks of the pressure readings in various areas of the cleanroom suite. The form prompts staff to check that the pressure differential from the grade B cleanroom to the changing area is within the required range. The DI is advised to update this form to include details of the expected pressure differentials across all areas of the suite, including those across the transfer hatch and from the changing area to the lobby, to help assure the DI that these differentials are also known and assessed against the regulatory requirements.
6.	PFE1a	SCT staff stated that supplies of Anticoagulant Citrate Dextrose Solution, Solution A (ACD-A) had been relocated on more than one occasion since the last inspection in an effort to ensure that the storage temperature remained within the manufacturer's specifications. The DI is advised to assess any risks associated with moving reagent(s) and the new storage environment(s) within the establishment's documented risk assessments.

7.	PFE5c	During a visual inspection of the theatre fridge used to temporarily store iliac vessels supplied by another HTA-licensed establishment, a build-up of ice was noted on the inner surfaces, and pooled water had collected on the lowest inner surface. It was further determined that the temperature measurements for this fridge were gradually increasing, although the temperature had not exceeded the specified range for the storage of vessels, and there were no vessels stored in the fridge at the time of the inspection. The DI was advised verbally during the inspection to contact the manufacturer of the fridge for advice in resolving this issue and to ensure that steps were taken to safeguard the quality and safety of any tissue that may require storage prior to its resolution.
8.	PFE5c	The DI is advised to ensure that the thermometer used to monitor the temperature of the room during apheresis has been calibrated so that the temperature data is accurate. The DI is further advised to review the establishment's fridge mapping data to help in determining the most appropriate locations for the temperature monitoring probe as well as any stored tissues and reagents.

Background

Birmingham Children's Hospital (the establishment) undertakes the processing, storage and distribution of heart valves, pulmonary patches and conduits in a dedicated cleanroom facility. The team undertaking these activities also manage the receipt and storage of a range of purchased tissues, which are released to the relevant hospital departments for use when requested.

The hospital's SCT service also operates under the establishment's licence, procuring PBSC, BM and DLI for autologous and allogeneic use. Processing and storage of procured cells, as well as the mandatory testing of donors, is undertaken by another licensed establishment under the terms of an SLA.

The establishment has been licensed by the HTA since August 2006 and this was the sixth site visit inspection. The most recent previous inspection took place in November 2017, with a follow-up visit in September 2018 to assess the suitability of the new apheresis facility (Waterfall House) and review documentation relating to CAPAs from the 2017 inspection.

Since the last inspection, the establishment has opened the new apheresis facility and appointed a new DI. The HVB has commenced testing heart valve donors for mandatory serology markers through a service level agreement with another licensed establishment, in order to achieve the regulatory requirement to undertake mandatory donor serological testing under the authority of a suitable licence issued by the HTA. In 2018 the establishment exported skin as the starting material for the manufacture of an advanced therapy investigational medicinal product (ATIMP). The export was in response to acute patient need and was granted emergency authorisation by the HTA prior to the export taking place.

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 a total of 121 standards in the Human Application sector, and establishment compliance against 109 of these standards was assessed during the inspection. Standards C1b, C2b, GQ1f, and PFE1d were not applicable. Standards GQ1q, r, s, GQ7e and f, GQ8d, PFE4f and D1a were not assessed. The 47 licensing standards associated with storage of relevant material under the Human Tissue Act (the HT Act) were not assessed during this inspection.

Review of governance documentation

The inspection included a review of documentation relevant to the establishment's licensable activities. This included the quality manuals of the HVB and SCT service, SOPs, patient information and clinical records, controlled forms, records of cleaning, servicing and calibration, temperature monitoring records, agreements with third parties, meeting minutes, reported incidents and adverse events, audit records, risk assessments and staff training records.

Visual inspection

The inspection team visited the HVB cleanroom suite and tissue and reagent storage areas, the vessel storage fridge in theatres, the new apheresis facility, the laboratory undertaking CD34 measurements for the SCT service, and the storage areas for reagents and consumables associated with bone marrow and apheresis activities.

Audit of records

The inspection team reviewed consent, donor selection, procurement, processing, and traceability records, and associated serology, microbiology and environmental monitoring results for three heart tissue processing events. Equivalent records associated with procurement of PBSCs from one autologous donor and bone marrow from one allogeneic donor were also reviewed. Records of traceability for three purchased bone items, two ophthalmic tissues and five units of purchased skin were reviewed and consisted of databases, patient records and care plans.

Meetings with establishment staff

The inspection included discussions with the DI (who is a Consultant Paediatric Intensivist), the SCT Quality Manager and a Haematology Consultant, who were both Persons Designated (PDs) under the licence, as well as members of the SCT specialist nursing team. The inspection team also held discussions with staff (including the relevant PD) undertaking the processing of heart tissues, management of the cleanroom suite and management of the systems associated with tissue purchased from other establishments.

Report sent to DI for factual accuracy: 24 December 2019

Report returned from DI: 14 January 2020

Final report issued: 24 January 2020

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.