Site visit inspection report on compliance with HTA licensing standards
Inspection date: **20-21 November 2019**

The Christie

HTA licensing number 11081

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
'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.

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

Site	Procurement	Processing	Testing	Storage	Distribution	Import	Export
The Christie	E/TPA	E		E	E/TPA		E

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

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

Mature Cell, MNC; DLI	Authorised	Authorised		Authorised	Authorised TPA		
Mature Cell, MNC; PBMCs	Authorised	Authorised		Authorised			Authorised TPA
Progenitor Cell, Haematopoietic, Cord Blood; Cord Blood		Authorised		Authorised			
Other; Tumour (ATMP)	Authorised TPA						

Licensed activities – Human Tissue Act 2004

Area	Storage of relevant material which has come from a human body for use for a scheduled purpose
The Christie	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 The Christie (the establishment) had met the majority of the HTA's standards, nine minor shortfalls were found against standards for Governance and Quality, and Premises, Facilities and Equipment.

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.		
s) Third party agreements specify that the third party will inform the establishment in the event of a serious adverse reaction or event.	The agreement between the establishment and the courier states that any adverse events must be communicated to the establishment. However, it does not stipulate that this must be within 24 hours of discovery.	**Minor**

GQ2 There is a documented system of quality management and audit.		
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.	Although an independent audit was carried out in 2019, it did not include all applicable standards. The audit covered only a small number of Governance and Quality standards.	**Minor**

GQ4 There is a systematic and planned approach to the management of records.		
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.	The establishment's documentation does not stipulate that all raw data have to be kept for 10 years "after use, expiry date or disposal of tissue and/or cells".	**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 003/2010.	The donor questionnaire does not contain questions about xenografts, and ingestion of, or exposure to, a substance (such as cyanide, lead, mercury, gold) that may be transmitted to recipients in a dose that could endanger their health.	**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.	During the inspection, procurement records for two donor lymphocyte infusions (DLI), which were collected independently of any other cells, were reviewed. It was noted that one donor did not undergo the mandatory serology testing in accordance with regulatory requirements. Establishment staff indicated that previous DLI donors were also not tested according to requirements.	**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 reactions, including documentation of any corrective or preventative actions.	The establishment has no procedure in place for reporting serious adverse events and reactions in the absence of the DI.	**Minor**
b) There is a system to receive and distribute national and local information (e.g. HTA regulatory alerts) and notify the HTA and other establishments as necessary of serious adverse events or reactions.	A review of the establishment's incident log identified a number of potential serious adverse events that were not reported to the HTA. For example: - samples from two bone marrow harvests were found to be contaminated with bacteria; and - a frozen bag containing stem cells broke while in storage and was subsequently disposed.	**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 anticoagulant used during apheresis is stored at ambient temperature. The manufacturer recommends a maximum storage temperature of 25°C. A review of temperature records showed the temperature in the apheresis suite and the storage room frequently ranges between 25 - 28°C. The establishment's documents do not contain adequate procedures and actions that should be taken when the anticoagulant has been stored above 25°C. In addition, the room temperature probes had been set to alarm at 27.7°C.	**Minor**

PFE5 Equipment is appropriate for use, maintained, quality assured, validated and where appropriate monitored.		
b) Critical equipment is maintained and serviced in accordance with the manufacturer's instructions.	The temperature probes used in the apheresis suite and storage room have been in use for over four years without being serviced or calibrated.	**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.	PFE3a	The establishment stores apheresis kits on open shelves next to a patient treatment area, which is overlooked by staff working at the reception desk. The DI is advised to risk assess this storage area because kits are potentially accessible to patients and visitors of the unit.

Background
The Christie is a large cancer treatment centre in Manchester. It is licensed under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended) for the procurement, processing, storage, distribution and export of cells for human application. The licence covers peripheral blood stem cells, bone marrow, cord blood, cells for DLIs, peripheral blood mononuclear cells (PBMCs) and tumour tissue. Donor serology testing and sterility testing of cell products are carried out under Service Level Agreements (SLAs) with separate HTA-licensed establishments.

The Christie has been licensed by the HTA since 2006. This was the seventh site visit inspection of the establishment; the most recent previous inspection took place in November 2017.

Since the previous inspection, the establishment has become licensed for the procurement, processing and export of PBMCs as starting material for Advanced Therapy Medicinal Products (ATMPs). In 2019, the establishment was licensed for the procurement of tumour material as ATMP starting material, but this activity has not yet commenced.

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. Compliance with 112 standards was assessed. Standards GQ8d, PFE4i and PFE4j were not reviewed. Standards C1b, C2b, GQ1f, GQ1n, GQ5e and PFE1d were not applicable.

The establishment is also licensed for the storage of relevant material under the Human Tissue Act 2004. The establishment does not currently store any material for a scheduled purpose. Therefore, compliance with the applicable standards was not reviewed during the inspection.

Review of governance documentation

The inspection included a review of policies and procedural documents relevant to the establishment's licensable activities. The inspection also included a review of equipment service contracts, records of servicing, temperature monitoring records, and agreements with third parties. The review of information relating to the quality management system included meeting minutes, incidents, audits, risk assessments, job descriptions, and staff training records.

Visual inspection

The inspection included a visual inspection of the apheresis suite and the associated storage room, the blood science laboratory where cell quality checks and flow cytometry are carried out, the clean room facility, and the cryostore.

Audit of records

The consent forms, procurement and processing records (if applicable) were audited for the following donors:

- two autologous donors;
- three allogenic donors (of which two were procured via a stem cell registry);
- two bone marrow donors;
- two PBMC donors; and
- two DLI donors. One donor did not have the mandatory serology sample taken on the day of procurement, or within seven days post donation (*see shortfall against GQ5b*). In addition, the documentation from the apheresis unit contained a checkbox, which is used to document that the mandatory serology blood has been taken; this was not completed for either of the two DLI donors.

Meetings with establishment staff

The inspection included interviews with the Stem Cell Laboratory Manager (who is the DI), the Corporate Licence Holder contact, the Collection Facility Director, the Lead Apheresis Nurse and relevant establishment staff involved with Quality Control and Governance systems.

Report sent to DI for factual accuracy: 13th December 2019

Report returned from DI: No factual accuracy or request for redaction comments were made by the DI.

Final report issued: 8th 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.