Site visit inspection report on compliance with HTA licensing standards
Inspection date: **16-17 October 2019**

Tissue & Cell Technologies Ltd

HTA licensing number 11020

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
Tissue and Cell Technologies Ltd	TPA	E/TPA	TPA	E	TPA		

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
Adipose; Adipose	Authorised TPA	Authorised	Authorised TPA	Authorised	Authorised TPA		

Skin; Skin	Authorised TPA		Authorised TPA				
Other; Hair Follicle	Authorised TPA	Authorised TPA	Authorised TPA	Authorised	Authorised TPA		
Musculoskeletal, Bone; Bone				Authorised			
Musculoskeletal, Tendon & Ligament; Tendons				Authorised			

Licensed activities – Human Tissue Act 2004

Area	Storage of relevant material which has come from a human body for use for a scheduled purpose
Tissue and Cell Technologies Ltd	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 Tissue & Cell Technologies Ltd (the establishment) had met the majority of the HTA's standards, seven 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

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.	In the event that the establishment's courier service is unavailable, establishment staff indicated they would transport tissue using personal vehicles as a contingency measure; the establishment's documented transport procedure did not reflect this. ***The establishment submitted evidence that this shortfall has been addressed prior to issue of the report. The HTA has assessed this information as satisfactory and considers this standard to be met.***	**Minor**

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 have to be communicated to the establishment “without delay”. However, the agreement does not include an instruction that adverse events must be reported to the establishment within 24 hours of discovery. ***The establishment submitted evidence that this shortfall has been addressed prior to issue of the report. The HTA has assessed this information as satisfactory and considers this standard to be met.***	**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.	If required, the establishment processes adipose tissue during weekends. Although recorded between Monday to Friday, staff do not record the pressure differentials in the clean room facility on weekend days if processing is taking place. ***The establishment submitted evidence that this shortfall has been addressed prior to issue of the report. The HTA has assessed this information as satisfactory and considers this standard to be met.***	**Minor**

GQ8 Risk assessments of the establishment's practices and processes are completed regularly and are recorded and monitored appropriately.		
a) There are documented risk assessments for all practices and processes.	In the event that the establishment's courier service is unavailable, establishment staff will transport tissue using personal vehicles as a contingency measure. This contingency procedure has not been risk assessed. ***The establishment submitted evidence that this shortfall has been addressed prior to issue of the report. The HTA has assessed this information as satisfactory and considers this standard to be met.***	**Minor**

PFE1 The premises are fit for purpose.		
a) A risk assessment has been carried out of the premises to ensure that they are fit for purpose.	The establishment does not formally carry out or request risk assessments to assess the suitability of the premises at the clinical sites where adipose tissue is procured or where procurement kits containing donor serological testing blood tubes are stored. ***The establishment submitted evidence that this shortfall has been addressed prior to issue of the report. The HTA has assessed this information as satisfactory and considers this standard to be met.***	**Minor**

PFE3 There are appropriate facilities for the storage of bodies, body parts, tissues, cells, consumables and records.		
d) There is a documented, specified maximum storage period for tissues and / or cells.	The establishment stores adipose tissue for two years via a contractual agreement which can be extended on request. However, the establishment has not specified and documented a maximum storage period for the tissue, or developed a procedure describing the action to take with regards to the release of tissue that is stored beyond any such maximum period. ***The establishment submitted evidence that this shortfall has been addressed prior to issue of the report. The HTA has assessed this information as satisfactory and considers this standard to be met.***	**Minor**

PFE5 Equipment is appropriate for use, maintained, quality assured, validated and where appropriate monitored.		
c) Equipment affecting critical processes and storage parameters is identified and monitored to detect malfunctions and defects and procedures are in place to take any corrective actions.	For several months in 2019, the temperature of the incubator used during testing for fungal contamination was running at an elevated temperature; 29^{o}C rather than within a 20^{o}C – 25^{o}C range. This issue was not detected because the alarm limits of the incubator's temperature monitoring system did not reflect the required temperature range. The establishment has not risk assessed if any results from the fungal contaminant testing were compromised and any effect that this may have on stored tissue products that were processed during this period. ***The establishment submitted evidence that this shortfall has been addressed prior to issue of the report. The HTA has assessed this information as satisfactory and considers this standard to be met.***	**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 sends a blood tube with the procurement kits to the sites where adipose tissue is harvested to collect a sample that is used for mandatory serological donor testing. The transport box includes a temperature logger which records the temperature of the kit between leaving the establishment to its return. The establishment routinely reviews the temperature data between tissue collection until receipt at the establishment. The DI is advised to also review the temperature data prior to the tissue procurement to help assure themselves that the blood collection tube has been stored at the temperature specified by the tube's manufacturer prior to its use.

Background

Tissue & Cell Technologies Ltd (formerly named Regenerys Ltd) has been licensed by the HTA since August 2006. This was the seventh inspection of the establishment. The most recent previous inspection took place in 2017.

Since the previous inspection, the establishment has ceased procurement of keratinocytes as a starting material for Advanced Therapeutic Medicinal Products. Since 2019, the establishment has been licensed to procure, process, perform donor testing, store and distribute hair follicles via a third party agreement with an unlicensed establishment.

The establishment's main activity is the procurement, processing, donor testing, storage and distribution of autologous adipose tissue, which is used in reconstructive surgery. The establishment is also licensed for the procurement of skin and donor testing of skin donors. Storage of bone and tendons as a contingency for another HTA-licensed establishment is also included in the establishment's 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 number of standards in the Human Application sector. Compliance with 112 standards was assessed. Standards C3a, C3b, GQ5e and GQ8d were not reviewed. Standards GQ1f, GQ1n, GQ5c, PFE1d and D2b were not applicable.

The establishment is also licensed for the storage of relevant material for use for a scheduled purpose under the Human Tissue Act 2004. The establishment currently stores very few samples of relevant material for research purposes. The consent forms for the samples being stored for research were reviewed. Compliance with the remaining applicable HTA standards was not reviewed during this inspection.

Review of governance documentation

The inspection included a review of documentation relevant to the establishment's licensable activities. This included policies and procedural documents, contracts for servicing of equipment and records of servicing, temperature monitoring data, agreements with third parties, donor records including records of procurement, processing and testing, meeting minutes, incidents, adverse events, audits, risk assessments, and staff training records.

Visual inspection

The inspection included a visual inspection of the establishment's processing facility, the cryostore, the room used for storage of consumables and in which fridges and incubators are located, and the office where documents are stored.

Audit of records

The procurement and processing records associated with six autologous adipose tissue donors were reviewed. Of the six donors, three had tissue released and used in treatment. The serology and microbiology test results were reviewed for all six donors and no

discrepancies were identified. In one processing record, the expiry date of a reagent had been recorded incorrectly. However, following a review of the batch records, this was corrected during the inspection.

Meetings with establishment staff
The inspection included discussions with the DI who is also the Technical and R&D Director. Additional interviews were also undertaken with the Head of Quality, the Corporate Licence Holder contact, a production scientist and the IT manager.

Report sent to DI for factual accuracy: 6th November 2019

Report returned from DI: 19th November 2019

Final report issued: 3rd December 2019

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.