Site visit inspection report on compliance with HTA licensing standards

Cryo-Store Ltd

HTA licensing number 12568

Licensed under the Human Tissue Act 2004 for the

- **storage of relevant material which has come from a human body for use for a scheduled purpose**

07 June 2017

Summary of inspection findings

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

Although the HTA found that Cryo-Store Ltd had met the majority of the HTA's standards, two minor shortfalls were found in relation to: (i) an internal audit system; and (ii) risk assessments of licensed activities.

Advice has been given relating to the Governance and Quality Systems and Traceability standards, as well as advice on licence management.

Particular examples of good practice are included in the concluding comments section of the report.

The HTA's regulatory requirements

Prior to the grant of a licence, the HTA must assure itself that the Designated Individual (DI) is a suitable person to supervise the activity authorised by the licence and that the premises are suitable for the activity.

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.

Its programme of site visit inspections to assess compliance with HTA licensing standards is one of the assurance mechanisms used by the HTA.

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. They are grouped under four headings:

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

This is an exception-based report: only those standards that have been assessed as not met are included. Where the HTA determines that there has been a shortfall against a standard, 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 provided.

HTA inspection reports are published on the HTA's website.

Background to the establishment

This report refers to the activities carried out by Cryo-Store Ltd (the establishment). The establishment was originally granted an HTA Human Application licence (HTA licensing number 11136) in September 2006 and was inspected by the HTA under this licence in July 2008. The Human Application licence was revoked in August 2010 and the current Research licence issued in September 2010. This was the first site visit inspection of the establishment under this licence. The current inspection was a routine site visit to assess whether the establishment is continuing to meet the HTA's standards.

The establishment is licensed under the Human Tissue Act 2004 (HT Act) for the storage of relevant material for use for a scheduled purpose. In this case, relevant material from living donors is being stored for the scheduled purpose of 'research in connection with disorders, or the functioning, of the human body'.

The DI supervising activities taking place under the licence is the General Manager, the Corporate Licence Holder (CLH) is Cryo-Store Ltd and the CLH Contact (CLHC) is the Business Development Manager. There are no Persons Designated (PDs) working under the licence (see *Advice*, item 1).

Cryo-Store is a privately held company that stores biological and clinical material for the pharmaceutical, biotechnology and healthcare industries. The company has two full-time

employees, supported by a part-time storage technician and consultants for quality assurance, information technology and accounting.

The establishment stores relevant material under contract (termed ‘master contracts’) with each of its clients. The master contract includes a declaration that appropriate and valid consent is in place. The establishment then creates ‘technical agreements’, which give detailed work instructions for each client. Clients include those involved in the manufacture of medicinal products and investigational medicinal products working under Good Manufacturing Practice (GMP).

The establishment stores a wide range of products, including cell lines, drug products, hormones, antibodies and viruses for clinical use. The establishment also stores small quantities of relevant material (whole blood and plasma) and other bodily material (serum; see *Advice*, item 7).

Receipt and release

Samples are received into the establishment in validated temperature-monitored dry shippers or dry ice containers. There are integrity checks of the sample and the temperature of the shipment packaging as well as checks of the paperwork. Non-conformances are managed by a specific procedure.

Samples are labelled by a unique identifier (bar code) created by the establishment in addition to any original identifiers provided by the clients. Sample identifiers and locations are recorded on the establishment’s electronic database.

When required, samples are returned to clients in temperature-monitored containers and there is a procedure for confirmation of receipt by the client.

Storage

The establishment is a purpose built storage facility housed within a secure compound. Access is via digital keypad and the facility is monitored by closed-circuit television (CCTV) and proximity sensing alarms, which are monitored by the security company.

The facility currently contains two lockable liquid nitrogen storage vessels (cryovessels), 21 lockable freezers (18 -80°C and three -20°C), nine lockable refrigerators and a dedicated area for controlled ambient temperature storage. Cryovessel, freezer and refrigerator space is available as a contingency.

As part of its compliance under GMP and Good Distribution Practice (GDP), the establishment is required to meet specific standards for the monitoring of storage facilities, including the regular temperature mapping of cryovessels, freezers and refrigerators.

All cryovessels, freezers and refrigerators are linked to continuous temperature-monitoring units, which feed into an automated, wireless callout system. Temperature excursions outside the set ranges trigger both local audible alarms and the callout system and the system is tested regularly. There are oxygen depletion monitors in the facility linked to an alarm system. The cryovessels are filled automatically from separate liquid nitrogen storage tanks, which are filled twice a week.

Disposal

Although most samples are returned to clients for disposal, the establishment occasionally disposes of non-conforming consignments. The establishment keeps a record of disposed samples in the paper records and on the electronic inventory.

Description of inspection activities undertaken

The timetable for the site visit inspection was developed after consideration of the establishment's previous inspection report, compliance update information and communications with the HTA. The inspection included a visual inspection of the site (sample receipt and storage areas), discussions and interviews with key staff, and a review of documentation. Interviews were held with the DI and the Storage Operations Manager. Audits of traceability were also carried out.

Traceability audits were performed on six separate samples. The samples were randomly selected on the database and labelling and location details were noted. They were then traced to the respective cryovessel, -80°C or -20°C freezer. There was full traceability, with no discrepancies noted.

Inspection findings

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

Compliance with HTA standards

Governance and Quality

Standard	Inspection findings	Level of shortfall
GQ2 There is a documented system of audit		
a) There is a documented schedule of audits covering licensable activities.	There is no internal audit system aimed at assessing the establishment's compliance against the full range of licensed activities. See *Advice*, item 3.	**Minor**
GQ6 Risk assessments of the establishment's practices and processes are completed regularly, recorded and monitored		
a) There are documented risk assessments for all practices and processes requiring compliance with the HT Act and the HTA's Codes of Practice.	There are Health and Safety risk assessments relating to sample handling procedures but there are no risk assessments for licensed activities. See *Advice*, item 6.	**Minor**

Advice

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

No.	Standard	Advice
1.	N/A	The DI is advised to consider appointing a PD to assist him in the role. This would be especially important on those occasions when the DI is absent. The HTA must be notified of such an appointment.

2.	GQ1d	In the establishment's monthly Quality Meetings, the DI is advised to consider including items such as standardisation of documents, changes to standard operating procedures (SOPs), audits and their findings, competence and training, management of adverse events, risk assessments, equipment maintenance and updates from the HTA (e.g. e-newsletter items).
3.	GQ2a, 2b	The DI is advised to consider developing an audit schedule that includes horizontal audits to ensure that SOPs accurately reflect current practices and vertical traceability audits, from records of receipt to release or disposal. The results of all audit findings, and actions taken, should be formally recorded and discussed at the Quality Meetings, to ensure continuing improvement of processes and practices. Audits currently performed by clients (approximately every two months) and the annual audit by the quality assurance consultant could be included in the audit schedule.
4.	GQ3a	The establishment only has competence-training records up to 2014. The DI is advised to ensure that staff competence and refresher training is up to date and is recorded on a regular basis.
5.	GQ5a, b	Although a central log of incidents is kept, the DI is advised to ensure that the full range of adverse events relating to human samples is captured. Actions taken as a result of the adverse event should be formally recorded and reviewed at the Quality Meetings. The HTA Code E Research Standards and Guidance document gives further guidance on this (pages 11-12): 'All establishments licensed by the HTA are required to have an internal system for reporting adverse events and, where necessary, instigating an investigation or root cause analysis. Clearly assigning responsibilities for incident management is important. As the DI is responsible for licensed activities at the establishment, there should be a process in place to allow them to be made aware of adverse events so that proper investigation and reporting can take place. There should be an adverse incident SOP detailing how adverse incidents are logged, reported, addressed and monitored. Although there is currently no requirement for establishments in the research sector to report adverse incidents to the HTA, if a DI has concerns about an adverse event, they are encouraged to contact us for further advice. Relevant examples of adverse events include: • specimen loss; • missing or incorrect documentation; • security breach; • abnormalities in storage temperature readings; • inappropriate disposal'.
6.	GQ6a-c	The HTA Code E Research Standards and Guidance document gives further guidance on this (pages 12-13): 'All establishments should identify the risks inherent in the key activities, and procedures should be developed in consideration of and to mitigate these potential risks where appropriate. Establishments may tend to focus risk

		assessments on health and safety issues which, in themselves, are not sufficient to meet our standards. DIs should also assess the risks associated with licensed activities. Documented risk assessments should include an evaluation of the level of the risk and, where appropriate, the mitigating actions identified and the level of residual risk remaining. Risk assessments should include the risks relating to the premises, practices and procedures connected with licensed activities, including: • receiving and/or storing specimens without appropriate consent documentation; • storing or using human tissue after consent withdrawal; • storage failure or other damage affecting human tissue quality for useful research; • loss of human tissue; • sample mix-up or loss of traceability; • transport of specimens to and from the establishment ; • security arrangements; • incorrect disposal. Risk assessments should be reviewed periodically (typically, every 1-3 years) and the actions to mitigate risks updated as necessary. Risk assessments should also be reviewed following an incident. By documenting risk assessments, staff are made aware of identified risks, which helps to prevent risks materialising and informs the development of procedures and relevant documentation'.
7.	T1b	For licensing and audit purposes, the DI may wish to consider distinguishing stored relevant material from other products in the tissue register. The DI may also wish to incorporate such distinctions within the technical agreements drawn up for each client.

Concluding comments

During the inspection, an area of good practice was noted:

- The company consists of a small team, which works well together.

There are a number of areas of practice that require improvement, including two minor shortfalls. The HTA has given advice to the DI with respect to the Governance and Quality Systems and Traceability standards, as well as advice on licence management.

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.

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.

Report sent to DI for factual accuracy: 5 July 2017

Report returned from DI: 25 July 2017

Final report issued: 9 August 2017

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: 08 June 2018

Appendix 1: HTA standards

The HTA standards applicable to this establishment are shown below; those not assessed during the inspection are shown in grey text. Individual standards that are not applicable to this establishment have been excluded.

Consent standards
C1 Consent is obtained in accordance with the requirements of the Human Tissue Act 2004 (HT Act) and as set out in the code of practice
c) Where applicable, there are agreements with other parties to ensure that consent is obtained in accordance with the requirements of the HT Act and the HTA's Codes of Practice.

Governance and quality system standards
GQ1 All aspects of the establishments work are governed by documented policies and procedures as part of the overall governance process
a) Ratified, documented and up-to-date policies and procedures are in place, covering all licensable activities. b) There is a document control system. c) There are change control mechanisms for the implementation of new operational procedures. d) Matters relating to HTA-licensed activities are discussed at regular governance meetings, involving establishment staff. e) There is a system for managing complaints.
GQ2 There is a documented system of audit
a) There is a documented schedule of audits covering licensable activities. b) Audit findings include who is responsible for follow-up actions and the timeframes for completing these.
GQ3 Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills
a) Qualifications of staff and all training are recorded, records showing attendance at training. b) There are documented induction training programmes for new staff. c) Training provisions include those for visiting staff. d) Staff have appraisals and personal development plans.
GQ4 There is a systematic and planned approach to the management of records
a) There are suitable systems for the creation, review, amendment, retention and destruction of records. b) There are provisions for back up / recovery in the event of loss of records. c) Systems ensure data protection, confidentiality and public disclosure (whistleblowing).

GQ5 There are systems to ensure that all adverse events are investigated promptly
a) Staff are instructed in how to use incident-reporting systems.
b) Effective corrective and preventive actions are taken where necessary and improvements in practice are made.
GQ6 Risk assessments of the establishment's practices and processes are completed regularly, recorded and monitored
a) There are documented risk assessments for all practices and processes requiring compliance with the HT Act and the HTA's Codes of Practice.
b) Risk assessments are reviewed regularly.
c) Staff can access risk assessments and are made aware of risks during training.

Traceability standards
T1 A coding and records system facilitates the traceability of bodies and human tissue, ensuring a robust audit trail
a) There is an identification system that assigns a unique code to each donation and to each of the products associated with it.
b) A register of donated material, and the associated products where relevant, is maintained.
c) An audit trail is maintained, which includes details of: when and where the bodies or tissue were acquired and received; the consent obtained; all sample storage locations; the uses to which any material was put; when and where the material was transferred, and to whom.
d) A system is in place to ensure that traceability of relevant material is maintained during transport.
e) Records of transportation and delivery are kept.
f) Records of any agreements with courier or transport companies are kept.
g) Records of any agreements with recipients of relevant material are kept.
T2 Bodies and human tissue are disposed of in an appropriate manner
a) Disposal is carried out in accordance with the HTA's Codes of Practice.
b) The date, reason for disposal and the method used are documented.

Premises, facilities and equipment standards
PFE1 The premises are secure and fit for purpose
a) An assessment of the premises has been carried out to ensure that they are appropriate for the purpose.
b) Arrangements are in place to ensure that the premises are secure and confidentiality is maintained.
c) There are documented cleaning and decontamination procedures.

PFE2 There are appropriate facilities for the storage of bodies and human tissue
a) There is sufficient storage capacity. b) Where relevant, storage arrangements ensure the dignity of the deceased. c) Storage conditions are monitored, recorded and acted on when required. d) There are documented contingency plans in place in case of failure in storage area.
PFE3 Equipment is appropriate for use, maintained, validated and where appropriate monitored
a) Equipment is subject to recommended calibration, validation, maintenance, monitoring, and records are kept. b) Users have access to instructions for equipment and are aware of how to report an equipment problem. c) Staff are provided with suitable personal protective equipment.

Appendix 2: Classification of the level of shortfall

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 HT Act or associated Directions.

1. **Critical shortfall:**

   A shortfall that poses a significant risk to human safety and/or dignity or is a breach of the Human Tissue Act 2004 (HT Act) or associated Directions

   or

   A combination of several major shortfalls, none of which is critical on its own, but which together could constitute a critical shortfall and should be explained and reported as such.

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

   (1) A notice of proposal being issued to revoke the licence

   (2) 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.

   (3) A notice of suspension of licensable activities

   (4) Additional conditions being proposed

   (5) Directions being issued requiring specific action to be taken straightaway

2. **Major shortfall:**

   A non-critical shortfall that:

   - poses a risk to human safety and/or dignity, or
   - indicates a failure to carry out satisfactory procedures, or
   - indicates a breach of the relevant CoPs, the HT Act and other relevant professional and statutory guidelines, or
   - has the potential to become a critical shortfall unless addressed

   or

   A combination of several minor shortfalls, none of which is major on its own, but which, together, could constitute a major shortfall and should be explained and reported as such.

   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, but which indicates a departure from expected standards.

   This category of shortfall requires the development of a corrective action plan, the results of either which will usually be assessed by the HTA by desk based or site visit 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 both the draft and final inspection report. You 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 desk-based or site-visit inspection.

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