Site visit inspection report on compliance with HTA licensing standards

Evotec UK Ltd

HTA licensing number 12585

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**

10 August 2017

Summary of inspection findings

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

Although the HTA found that Evotec UK Ltd (the establishment) had met the majority of the HTA's standards, three minor shortfalls were found against the Governance and quality (GQ) systems standards. The shortfalls were in relation to HTA-related governance meetings, audit and risk assessments relating to human tissue. Advice has been also been given relating to the GQ, Traceability (T) and Premises, Facilities and Equipment (PFE) standards.

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 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 Designated Individual 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 Evotec UK Ltd (the establishment). The establishment has been licensed since June 2011 and was last inspected in May 2013. This was the second site visit inspection.

The establishment is an international contract research organisation that aims to deliver drug discovery on behalf of pharmaceutical and biotechnology companies in the UK. The company's headquarters are located in Hamburg and the organisation has more than 1,200 employees worldwide. The establishment currently employs approximately 250 staff and provides 11 different drug discovery services, including Drug Metabolism and Pharmacokinetics (DMPK). The DMPK group imports and uses relevant material. The research predicts hepatic clearance of new drug formulations in high throughput screening or in low clearance assays.

The establishment stores hepatocytes from deceased donors under the Human Tisse Act 2004 (HT Act) for use in the scheduled purpose of 'research in connection with disorders, or the functioning, of the human body'. Hepatocytes are supplied as single donations or pooled donations from multiple donors and material is imported from two suppliers based in the United States of America (USA). The donor characteristics are screened by the suppliers and the establishment ensures appropriate consent has been sought through a Tissue Supply Agreement (TSA).

The DI supervising activities taking place under the licence is the DMPK Team Leader, the (Corporate) LH (CLH) is Evotec UK Ltd and the CLH Contact (CLHc) is the Chief Operating Officer. The establishment has no Persons Designated (PDs) listed on the licence.

Receipt, labelling and storage

End users (scientists within the DMPK group) order human tissue through the establishment's purchasing department. The supplier arranges, and is responsible for, all courier transport arrangements. The stores department receives human tissue and the DMPK group are emailed when samples have arrived. All samples are delivered in liquid nitrogen transport dewars.

Two scientists from the DMPK group collect the material from stores. All samples are previously labelled by the supplier with a lot number. The samples are stored at the establishment in liquid nitrogen cryovessels within storage canes. Each cane is labelled manually with the unique identifier at the corresponding position of the sample. However, the sample vial is not itself labelled (see *Advice,* item 8). The details of the sample are logged in the Human Tissue Trace spreadsheet.

At the time of inspection, the establishment was storing approximately 40 vials of hepatocytes and this material is regularly used. The cells are stored in three cryovessels: one in the cell culture laboratory and two in the main laboratory where screening takes place. The samples are split into three cryovessels to provide contingency in case of a storage failure, and also to

facilitate stock rotation. New samples are ordered when stock from one of the cryovessels has been exhausted. The DI is notified of all non relevant material, such as plasma, that is stored at the establishment.

Liquid nitrogen levels of the cryovessels are checked at a set time and day every week and the integrity of the dewars is also assessed. The cryovessels are refilled from the main storage tank which is housed externally (see *Advice,* item 9). Each dewar has an audible alarm and a remote wireless call-out system which alerts key staff when liquid nitrogen levels fall below a set level, or when the storage temperature increases to above -175°C. Animal and human tissue are stored separately.

Disposal

Human tissue samples are used to exhaustion and disposed of safely and in accordance with the HTA's requirements. Material delivered in inappropriate storage conditions or where poor viability has been identified are also disposed of accordingly. End users are responsible for disposing of tissue in the appropriate waste stream and logging the disposal against the associated experiment number or reason for disposal. Waste is collected by an external company and incinerated.

The inspection process

The timetable for this site inspection was developed after consideration of the establishment's previous inspection report, compliance update information and communications with the HTA since the last inspection. The inspection included a visual inspection of the site (two research laboratories), discussions with the DI, a DMPK scientist, the Health and Safety Manager and a documentation review.

Forward and reverse traceability audits were performed on 12 samples from commercial suppliers stored in cryovessels and selected at random from the Human Tissue Trace spreadsheet. Full traceability was found. All TSA agreements were also checked for evidence of appropriate donor consent.

Inspection findings

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

Compliance with HTA standards

Governance and quality systems

Standard	Inspection findings	Level of shortfall
GQ1 All aspects of the establishments work are governed by documented policies and procedures as part of the overall governance process		
d) Matters relating to HTA-licensed activities are discussed at regular governance meetings, involving establishment staff.	Although laboratory meetings are held, matters relating to HTA- licensed activities are not formally discussed at regular, scheduled meetings. *See Advice, item 4.* *The establishment provided documentary evidence to address this shortfall prior to the issue of the final report. The HTA has assessed this evidence as satisfactory to address this shortfall.*	**Minor**
GQ2 There is a documented system of audit		
a) There is a documented schedule of audits covering licensable activities.	The DI performs six monthly stock inventory checks. However, there is no formalised, documented system of audit aimed at assessing the establishment's compliance against the HTA's standards. *See Advice, item 5.* *The establishment provided documentary evidence to address this shortfall prior to the issue of the final report. The HTA has assessed this evidence as satisfactory to address this shortfall.*	**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; however the wider risks associated with licensed activities have not been documented. *See Advice, item 7.* *The establishment provided documentary evidence to address this shortfall prior to the issue of the final report. The HTA has assessed this evidence as satisfactory to address this shortfall.*	**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 her in the role. This would be especially important for those occasions when the DI is absent. The HTA must be notified of such an appointment, including contact details and job titles.
2.	GQ1(a)	The HTA encourages establishments to have an overarching quality document that provides an overview of the establishment's main purpose, organisation and structure and approach to governance and quality. This document should be accessible to all staff involved in licensed activities.
3.	GQ1(b)	During the inspection, variances in document control were observed. For example, the *Code of Conduct* as part of the quality documentation was neither dated nor version controlled. The DI is advised to ensure that governance documents include: • Revision history and version number; • 'Effective from' date; • Review date (at least every three years); • Pagination; • Author and reviewer name. This is to ensure all documents are regularly reviewed and updated as necessary and the most recent versions are in use.

4.	GQ1(d)	All staff working under the HTA licence should be aware of the governance arrangements in place, and they should be represented at governance meetings. Overall governance processes should be supported by regular meetings with staff at the establishment who are engaged in licensed activities. Meetings can be used to discuss items such as the standardisation of documents, changes to standard operating procedures (SOPs), audits and their findings, competence and training, management of adverse events, risk assessments and updates from the HTA (e.g. e-newsletter items). Formal meetings should be minuted and the actions should be noted and followed up. Documented minutes of meetings should be distributed to all relevant staff to help to ensure that they are aware of all important information relating to licensed activities at the establishment.
5.	GQ2(a)	The DI undertakes six monthly storage stock inventories to routinely check and update the inventory of human tissue. The DI is advised to expand these to include vertical audits of records and specimens to ensure samples are fully traceable from the TSA to disposal. The audit schedule should also include horizontal audits to ensure that SOPs accurately reflect current practices, and to identify areas for improvement. The results of all audit findings, and actions taken, should be formally recorded and discussed at the governance meetings, to ensure continuing improvement of processes and practices. Audits should be carried out on a periodic basis, or following a change in process
6.	GQ5(a)	The DI is advised to include within the *IOP/SF/0068 Procedures for Working with Human Tissue (section 10)* details of how adverse events are logged, reported, addressed and monitored to ensure that all staff are aware of adverse events so proper investigation and reporting can take place. Relevant examples of adverse events include: • specimen loss; • missing or incorrect documentation; • security breach; • abnormalities in storage temperature readings; • inappropriate disposal.
7.	GQ6(a)	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;

		• storage failure or other damage affecting human tissue quality for useful research; • loss of human tissue; • sample mix-up or loss of traceability; • 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.
8.	T1(a)	When storing hepatocytes, the cane housing the samples rather than the vial itself is labelled with unique identifiers. This is due to practical reasons in relabelling vials in cryostorage. The DI is advised to risk assess this process to ensure all mitigating controls are in place to avoid a loss of sample traceability.
9.	PFE1(a)	The liquid nitrogen dewars are regularly refilled each week by transporting the cryovessels to the main liquid nitrogen store. The DI is advised to risk assess this procedure to ensure all mitigating controls are in place.

Concluding comments

During the inspection, a number of strengths were noted:

- The DMPK group is a small team of people who seem to work well together.
- There is a commitment within the establishment, and the organisation as a whole, to implement a more robust quality management system.

There are a number of areas of practice that require improvement, including three minor shortfalls. The HTA has given advice to the DI with respect to the Governance and quality systems, Traceability and Premises, facilities and equipment standards, as well as advice on licence management.

The HTA requires the Designated Individual 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 September 2017

Report returned from DI: 18 September 2017

Final report issued: 4 October 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: 07 November 2017

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 which 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.
C2 Staff involved in seeking consent receive training and support in the essential requirements of taking consent

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 which 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.
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 which 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 which will usually be assessed by the HTA either by desk based or site visit.

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.