Licence application assessment visit report on compliance with HTA licensing standards

Cambridge Epigenetix Limited

HTA reference number 12670

Application to be 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**

6 October 2017

Summary of inspection findings

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

Although the HTA found that Cambridge Epigenetix Limited had met the majority of the HTA's standards, one minor shortfall was found in relation to documented risk assessments.

Particular examples of strengths and 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 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

Cambridge Epigenetix Limited (the establishment) is a research and development company working in the field of epigenetic modifications as biomarkers and for development of clinical diagnostic kits.

The establishment moved to its current premises in August 2017, which include purpose-designed laboratory facilities. The establishment has applied for a HTA licence for storage of relevant material which has come from a human body for use for scheduled purposes. The establishment plans to increase its research activities to include use of human tissue samples with the aim of developing and characterising epigenetic modifications as potential biomarkers for disease.

The establishment has facilities for storage of samples in fridges, -80°C freezers, liquid nitrogen tanks and at room temperature. The establishment plans to store all samples under the licence in one secure laboratory and in storage containers separate to non-human samples. Temperature-controlled storage units are connected to an automated alarm system to alert staff of deviations from the set acceptable temperature ranges, including a call-out notification procedure (refer to Advice, item 16). The establishment has contingency arrangements for back-up on-site temperature-controlled storage and emergency power supply (refer to Advice, item 17).

The establishment plans to acquire samples from commercial, third party organisations and collaborators at academic organisations; this means that staff at the establishment will not be involved with seeking consent from donors directly (refer to Advice, item 1). The establishment's procedures require staff to obtain approval from the DI to acquire human samples for storage and use at the establishment. The approval process will include checks on the documentation and consent statements from the organisations supplying samples to provide assurance that consent has been sought in accordance with the regulatory requirements (refer to Advice, items 2 and 3). The approval process will be documented and a centralised record will be kept of collections of samples stored under the HTA licence.

All human samples will be anonymised prior to being transported to the establishment. Samples will be assigned a unique identification code to track sample receipt, storage, use, transport off site and disposal (refer to Advice, item 11). The establishment may transfer samples to other HTA-licensed establishments for specialist analysis (refer to Advice, item 13). The establishment will use paper forms and an electronic database to record details of sample traceability. The establishment has plans to implement an electronic Laboratory Information Management System (LIMS) for tracking samples, in the near future.

Description of inspection activities undertaken

This report describes a licence application assessment site visit to assess the suitability of the establishment to hold a HTA licence. The suitability of the proposed DI and Licence Holder were assessed. The inspection included: review of the establishment's procedures for conducting activities under the licence; meetings with staff; visual inspection of the areas where it is planned that samples will be stored under the licence; and audits of sample traceability.

The establishment's procedures for sample traceability are the same for all human samples, irrespective of whether or not they are subject to the licensing requirements of the HT Act. Audits of sample traceability were conducted of samples stored at the establishment at the time of the inspection to assess the sample traceability procedures. Audits were conducted of thirteen samples from two donors, including records of sample receipt, traceability and assurance of consent. Audits were also undertaken of sample disposal. These audits did not identify any discrepancies in sample traceability or records.

Inspection findings

The HTA found the proposed Licence Holder, proposed 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
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.	Although the establishment has a procedure for conducting risk assessments, there are no documented risk assessments of the risks associated with the practices and processes requiring compliance with the HT Act and the HTA's Codes of Practice. *Refer to Advice, item 10.*	**Minor**

Advice

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

No.	Standard	Advice
1.	C1(a)	In the event that the establishment considers obtaining samples from donors directly, the proposed DI must ensure that appropriate policies and procedures are in place to govern this activity. Further information on the consent requirements of the HT Act can be found in the HTA's Codes of Practice, the current versions of which were published in April 2017 and are available on the HTA's website. The two recommended Codes are: Code of Practice A – Guiding Principles and Fundamental Principle of Consent; and Code of Practice E – Research.
2.	C1(c)	The proposed DI is advised to review the template for technical agreements which will be used with organisations supplying human samples to strengthen the assurance that valid and appropriate consent has been obtained for the storage and use of samples in accordance with the requirements of the HT Act.
3.	C1(c)	The proposed DI may wish to consider introducing a checklist to document the checks that will be performed on the consent status of samples as part of the establishment's procedure to approve samples being obtained to be stored under the licence. This will help to ensure that the approval process is conducted in a consistent manner and will provide further assurance that consent has been given in accordance with the regulatory requirements for all samples to be stored under the licence. The proposed DI is advised to consider including review of blank consent forms and participant information sheets as part of this process. The proposed DI is also advised to ensure that any restrictions on the consent for the use of samples are detailed on the sample traceability databases. This will help to ensure that samples are stored and used in accordance with the consent given.
4.	GQ1(a)	The establishment has an SOP for management of samples stored under the licence. The proposed DI is advised to review this document to ensure that it provides sufficient details of procedures. This will help to ensure that procedures are conducted in a consistent manner and in accordance with the HT Act and the HTA's Codes of Practice. *Refer to Advice, item 5.*
5.	GQ1(a)	The proposed DI is advised that the exception set out in the HT Act 2004 (Ethical Approval, Exceptions from Licensing and Supply of Information about Transplants) Regulations 2006 that allows human tissue held for a specific research project to be stored on premises without a HTA licence only applies where the project has been approved by a recognised research ethics committee (REC). The proposed DI is advised to include the definition of a recognised REC in the establishment's SOP for management of samples under the HTA licence to ensure that staff are aware of the requirements of the HT Act and associated regulations. Further information on the licensing requirements in this regard can be found in the HTA's Code of Practice E – Research (paragraphs 86 – 90 and 124 – 125), which was published in April 2017 and is available on the HTA's website.

6.	GQ1(d)	The proposed DI is advised to include matters relating to the licence on the agenda for the relevant committee meetings to help ensure that there is appropriate oversight of the licence. All staff working under the licence should be aware of the governance arrangements in place, and they should be represented at governance meetings. Minutes of governance meetings should be circulated to all relevant staff to help to ensure that they are aware of all important information relating to activities conducted under the licence.
7.	GQ2(a)	The establishment's audit schedule includes audits of licensed activities. The proposed DI is advised to consider introducing audit templates to help to ensure that audits cover all licensed activities, including consent documentation and disposal. Further guidance on audits can be found in the HTA's research sector licensing standards and guidance document, which is available on the HTA's website.
8.	GQ3(a)	The proposed DI is advised to ensure that all staff involved in undertaking licensed activities are aware of the requirements of the HT Act and the HTA's Codes of Practice.
9.	GQ5(a)	The proposed DI is advised to include details in the SOP for adverse events of the types of events that should be reported via the establishment's internal procedures. Examples of adverse events include, but are not limited to: • consent not sought in accordance with the HT Act requirements; • sample used not in line with consent given; • specimen loss; • missing or incorrect documentation; • security breach; • abnormalities in storage temperature; and • incorrect or inappropriate disposal.
10.	GQ6(a)	To address the shortfall against standard GQ6(a), the proposed DI should ensure that documented risk assessments cover all of the practices and processes requiring compliance with the HT Act and the HTA's Codes of Practice. In particular, the proposed DI should ensure that the following risks have been assessed: • receiving and/or storing specimens without appropriate consent documentation; • storing or using human tissue after consent withdrawal; • loss of human tissue; • sample mix-up or loss of traceability; • transport of specimens to and from the establishment; and • incorrect disposal. Further guidance on risk assessments of activities conducted under the licence can be found in the HTA's research sector licensing standards and guidance document, which is available on the HTA's website.
11.	T1(a)	The proposed DI is advised to ensure that all samples are labelled with a unique identification code, including where there are multiple samples within a batch. This will help to ensure that sample traceability is maintained where there are multiple samples within a batch. This may become more important to help to ensure traceability of samples is maintained in the event that more samples are stored at the establishment.

12.	T1(c)	The proposed DI is advised to consider labelling storage units to indicate that they contain human samples stored under the licence and with the reference number. This will help to ensure that sample traceability records accurately reflect storage locations and that human and non-human samples are stored appropriately.
13.	T1(g)	The proposed DI is advised that if human samples are to be transferred to other organisations, there should be a documented procedure and risk assessment for transport of samples. There should also be a formal transfer agreement which defines the transport procedures and responsibilities of each organisation for the samples, including to ensure that samples are stored and used in accordance with the requirements of the HT Act and the consent obtained.
14.	T2(a)	The proposed DI is advised that it is good practice for human tissue to be bagged separately from clinical waste for disposal. Further information on disposal of human tissue can be found in the HTA's Code of Practice E – Research (paragraphs 127 – 130), which was published in April 2017 and is available on the HTA's website.
15.	T2(b)	The proposed DI is advised to review the SOP for management of samples under the licence to describe the details of disposal that must be recorded. This will help to ensure that the establishment meets the HTA licensing standards in the event that they dispose of samples under the licence in the future.
16.	PFE2(c)	The proposed DI is advised to ensure that storage temperature monitoring arrangements are documented. This will help to ensure that staff are aware of the temperature monitoring arrangements and the actions to be taken in the event of an alarm. The proposed DI is advised to implement formal tests of storage temperature alarms. This will help to ensure that the alarm is functioning as expected. The proposed DI is also advised to ensure that temperature records are monitored for trends. This may help staff to identify when storage conditions may be deteriorating and might alert staff to impending equipment failure.
17.	N/A	The proposed DI is advised to label the electrical plugs of the storage units to ensure that they are not disconnected or switched off inadvertently.
18.	N/A	The proposed DI is advised to nominate Persons Designated (PDs) working under the licence to help to ensure oversight of licensed activities. In accordance with standard condition 11 (Annex B) of the licence, PDs can be added to the licence by notifying the HTA in writing of the name of the proposed PD. This can be done by email to licensing.enquiries@hta.gov.uk.

Concluding comments

This report describes the licence application assessment of the suitability of Cambridge Epigenetix Limited to be licensed under the HT Act for storage of relevant material which has come from a human body for use for scheduled purposes.

Some areas of good practice were identified during the inspection. The establishment has purpose-designed laboratory facilities with robust temperature monitoring and alarming arrangements for storage units. The establishment is developing a good quality management system and has a Quality Assurance team which is supported by a consultant with expertise in this field. The establishment demonstrated a commitment to compliance with the requirements of the HT Act and the advice given by the HTA.

The HTA found the proposed DI and Licence Holder to be suitable. One minor shortfall against the HTA standards was identified. 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 shortfall identified during the site visit.

Prior to issue of the report, the establishment submitted evidence of the corrective and preventative actions implemented to address the shortfall. Based on information provided, the HTA is satisfied that the establishment has taken sufficient actions to correct the shortfall during the site visit. The HTA will issue a HTA licence offer to the establishment.

Report sent to DI for factual accuracy: 19 October 2017

Report returned from DI: 27 October 2017

Final report issued: 27 October 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.

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.
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 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.