Site visit inspection report on compliance with HTA licensing standards

Oxford Biotherapeutics Ltd

HTA licensing number 12539

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**

16 May 2017

Summary of inspection findings

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

Although the HTA found that Oxford Biotherapeutics Ltd (the establishment) had met the majority of the HTA's standards, six minor shortfalls were found across all four groups of the standards.

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 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 Designated Individual are set down in Section 18 of the Human Tissue Act 2004 (HT Act). 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

Oxford Biotherapeutics Ltd is an international biotechnology company which aims to develop antibody-drug conjugates to treat cancer. The establishment uses human tissue samples with the aim of identifying and characterising molecular targets for treatment of cancer.

The establishment is licensed by the HTA under the HT Act for the storage of relevant material which has come from a human body for use for a scheduled purpose. The establishment stores human samples for use for the scheduled purpose of 'research in connection with disorders, or functioning, of the human body'.

The establishment has been licensed by the HTA since June 2009. The establishment was last inspected by the HTA in April 2014. This report describes the second routine inspection of the establishment. Since the last inspection, the establishment employs a larger number of staff and has changed its procedures to now use fresh samples of human tissue and cells.

The establishment acquires the majority of human samples from commercial, third party organisations and the majority of samples are imported. The establishment has received one batch of human samples from a non-commercial, third party organisation in England. The establishment requires that researchers obtain approval from the DI to acquire human samples for storage and use at the establishment. The approval process includes checks on the documentation and agreements with third party organisations supplying human samples to provide assurance of ethical approval and that consent has been sought in accordance with the regulatory requirements. This approval process is documented and a centralised record is kept of all collections of samples stored under the HTA licence.

All samples stored at the establishment at the time of the inspection were obtained from living donors. All human samples are stored separately to non-human tissues.

The establishment receives fresh or frozen human samples for use in research assays. Cells are collected from fresh tissue samples at varied time points and either used in assays or stored for future use. At the time of the inspection, the establishment was storing 44 frozen human samples, including seven samples stored in a -80°C freezer and 37 samples stored in a liquid nitrogen tank. The -80°C freezer is secured and in a secure laboratory area. An automated alarm is triggered in the event of a deviation from the set acceptable temperature ranges (see Advice, item 14). The temperature alarm is sounded locally during normal working hours and there is a call-out notification procedure in the event that the alarm is triggered outside of normal working hours. The liquid nitrogen storage tank is secured and in a secure area outside the main building. The establishment does not monitor the storage conditions of the liquid nitrogen tank (see shortfall against standard PFE2(c)). The establishment has contingency arrangements for temperature-controlled storage.

The establishment is also storing a collection of 3619 tissue samples on microscope slides. These samples are stored in a secured cabinet in a secure laboratory. At the time of the inspection, these samples were archived and stored for potential future use.

The DI and Persons Designated (PDs) maintain oversight of samples stored under the licence. All human samples are anonymised prior to being transported to the establishment and the establishment does not hold any patient identifiable information. All human samples stored at the establishment are assigned a unique identification code, which is used to track sample receipt, storage, use, distribution and disposal. Not all samples are labelled with the unique identification code assigned by the establishment; some samples are tracked in storage using the identification code assigned by the supplier (see Advice, item 10). The establishment uses an electronic Laboratory Information Management System (LIMS) to provide traceability of samples. The establishment also uses forms to record details of sample receipt, use, distribution and disposal. Completed forms are stored on an electronic document management system and linked to the LIMS entry for each sample. The establishment also uses an electronic database as a secondary traceability record for samples stored in the liquid nitrogen tank.

The establishment disposes of human samples by incineration. Samples are bagged separately from other waste and stored in an intermediate storage area prior to transfer to the waste contractor for disposal. Disposal is recorded on a disposal form and in LIMS.

Samples may be distributed to the establishment's premises in the USA. Distribution is recorded on a form and in LIMS.

Description of inspection activities undertaken

The inspection timetable was developed in consideration of the activities conducted under the licence, compliance update information, discussions with the DI and the findings of the previous inspection. The inspection included review of the establishment's procedures for conducting activities under the licence and interviews with staff. The inspection also included a visual inspection of the areas where samples are stored under the licence and audits of sample traceability. Audits of the following samples were conducted:

- four slides from sample to record and four slides from record to sample;
- all seven samples stored in the -80°C freezer, including LIMS records and sample receipt forms;
- nine samples stored in liquid nitrogen, seven samples from record to sample and two samples from sample to record, including the sample database and LIMS records;
- disposal records for five samples, including LIMS records and disposal forms;
- records of use of four samples, including LIMS records and sample use forms.

A minor discrepancy was identified with the traceability of one sample, where the storage location recorded in LIMS was incorrect (see Advice, item 5). One sample was incorrectly recorded in LIMS as not being of human origin and this resulted in this sample not being included in the establishment's manifest of human samples (see Advice, item 5). One disposal record did not include the reason for disposal (see shortfall against standard T2(b)).

The material transfer agreement for one batch of samples did not provide 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 (see shortfall against standard C1(c)).

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

Consent

Standard	Inspection findings	Level of shortfall
C1 Consent is obtained in accordance with the requirements of the Human Tissue Act 2004 (HT Act) and as set out in the HTA's Codes 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.	The material transfer agreement for samples from five donors transferred to the establishment from a third party organisation does not provide 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.	**Minor**

Governance and Quality

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.	The DI meets with the PDs on a regular basis; however, matters relating to HTA-licensed activities are not discussed at regular governance meetings. *See Advice, item 4.*	**Minor**
GQ2 There is a documented system of audit		
b) Audit findings include who is responsible for follow-up actions and the timeframes for completing these.	The establishment has conducted audits of samples stored under the licence on an ad hoc basis. The establishment's standard operating procedure (SOP) for audits covering licensed activities does not include details of the procedures for conducting audits or the records of audits that should be documented. Records of the audits do not include details of the audit findings, follow up actions required and completion of these. *See Advice, items 5 and 6.*	**Minor**
GQ5 There are systems to ensure that all adverse events are investigated promptly		
b) Effective corrective and preventive actions are taken where necessary and improvements in practice are made.	The establishment's SOP for adverse events does not include details of the procedure for investigating adverse events and records of adverse events that should be documented. Records of adverse events do not always include details of follow up actions required and completion of these. Completion of corrective and preventative actions cannot be evidenced for all adverse events.	**Minor**

Traceability

Standard	Inspection findings	Level of shortfall
T2 Bodies and human tissue are disposed of in an appropriate manner		
b) The date, reason for disposal and the method used are documented.	The establishment's SOP for disposal does not include details for documenting the date, reason for disposal and the method used. Although in some cases the reason for disposal is recorded on in the comments section on disposal worksheet, this is not done consistently. *See Advice, item 12.*	**Minor**

Premises, Facilities and Equipment

Standard	Inspection findings	Level of shortfall
PFE2 There are appropriate facilities for the storage of bodies and human tissue		
c) Storage conditions are monitored, recorded and acted on when required.	The establishment does not monitor the storage conditions of the liquid nitrogen tank. The liquid nitrogen tank is located in an area outside the main building and so any issues with this storage facility may go unnoticed by staff. This represents a potential risk to the integrity of samples stored in the liquid nitrogen tank. *See Advice, item 14.*	**Minor**

Advice

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

No.	Standard	Advice
1.	C1(c)	The DI is advised to ensure that any consent restrictions on the use of samples are detailed on the sample management records in LIMS. This will help to ensure that samples are stored and used in accordance with the consent given.

2.	GQ1(a)	The DI is advised to review the documented procedures and policies to ensure that they reference the latest versions of the HTA Codes of Practice and standards. This will help to ensure that staff are aware of the Codes of Practice and standards and refer to the most up-to-date versions of these. The DI is advised to ensure that documents include references to all relevant policies and procedures. This will help to ensure that staff are aware of all policies and procedures relating to the licence. The DI is also advised to consider including links to documents referenced in procedures and policies to ensure that staff can easily access these.
3.	GQ1(b)	The DI is advised to ensure that all documents relating to activities conducted under the licence are subject to the establishment's document control procedures. The DI is also advised to ensure that where sample traceability databases are printed, the printed document includes the date of printing so that it is clear whether it is the most up-to-date version of the database. The DI is advised to ensure that a consistent system for recording dates is used for all records. This will help to avoid potential confusion caused by use of different formats for recording dates.
4.	GQ1(d)	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 documented, including timelines for identified actions, and followed up. Minutes 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. The DI is also advised to document decisions made in laboratory group meetings in relation to matters concerning the licence. This will also help to ensure that decisions relating to governance of the licence are recorded.
5.	GQ2(a)	The DI is advised to ensure that the audit schedule includes vertical audits of records and samples, from consent documentation to disposal. Records should be audited regularly to ensure completeness, accuracy and legibility. The DI should ensure that audits include all sample traceability records, including sample traceability databases and forms. This will help to highlight any anomalies in these records and will provide assurance to the DI that documentation is accurate. Audits should also ideally include horizontal audits of processes against documented procedures to ensure that SOPs accurately reflect actual practices and to identify areas for improvement. Audits should be undertaken on a periodic basis and following changes to processes; for example, when sample handling processes are changed.
6.	GQ2(b)	The DI is advised that all audit findings and related corrective and preventative actions should be recorded, including timeframes for completion of actions and confirmation that all required actions have been completed. The DI may wish to consider using a form to record audits. This will help to ensure that details of audits are consistently recorded and followed up.
7.	GQ3(a)	The DI is advised to ensure that all staff working under the licence receive refresher training in the requirements of the HT Act, the HTA Codes of Practice and the establishment's local procedures. The DI is also advised to ensure that all training is recorded so that the training staff have undertaken is evidenced and can be monitored.

8.	GQ4(a)	The DI is advised to ensure that the procedures for record management are documented, including details of the standard review periods for policies and procedures relating to the activities conducted under the HTA licence. The DI is advised to ensure that written amendments to records are undertaken in a consistent manner, including detailing the date and signature of the person making the amendment. This will help to ensure that the traceability of records is maintained and that staff use the most up-to-date version of records.
9.	GQ6(a)	The DI is advised to ensure that risk assessments relating to activities conducted under the licence accurately reflect the establishment's procedures. This will help to ensure that risks have been appropriately assessed and acted upon.
10.	T1(a)	Although all samples are assigned a unique identification code, some samples are not labelled with this code and are tracked in storage using the identification code assigned by the sample supplier. The supplier's sample identification code is not unique to every sample within a batch in every case. The DI may wish to consider revising the sample labelling procedure to ensure that all samples are labelled with the unique identification code assigned by the establishment. This will help to ensure that sample traceability is maintained where there are multiple samples in a batch labelled with the batch identification code. 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.
11.	T1(c)	The DI is advised to consider labelling storage units to indicate that they contain human samples stored under the licence and with the storage identification number. This will help to ensure that sample traceability records accurately reflect storage locations. This will also help to ensure that human and non-human samples are stored separately.
12.	T2(b)	The DI is advised to review the form used to record sample disposal to include a section to record disposal reason. This will help to ensure that staff are aware that the reason for disposal of samples being stored under the licence must be recorded to meet the HTA licensing standards. Records of the reason for sample disposal will help the DI to analyse trends, which may help to inform the establishment's practices relating to human samples.
13.	PFE1(c)	The establishment undertakes cleaning and decontamination of storage facilities as required. The DI is advised to ensure that this procedure is documented and that records of cleaning and decontamination of storage facilities are maintained.
14.	PFE2(c)	The 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 DI is advised to implement formal tests of storage temperature alarms. This will help to ensure that the alarm is functioning as expected. The 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. This is particularly important as, although staff at the establishment perform limited preventative maintenance on the freezers, the freezers are not regularly serviced.
15.	N/A	A copy of the licence is displayed in the building's central entrance area. The DI is asked to display a copy of the HTA licence in all areas where samples are being stored under the licence. This will help to raise awareness that samples are being stored under the licence.

Concluding comments

This report outlines the second, routine HTA site visit inspection of Oxford Biotherapeutics Ltd. Although six minor shortfalls were identified, a number of areas of good practice were observed during the inspection, including:

- The DI has nominated PDs, who undertake key activities under the licence. The DI and PDs demonstrated willingness to work together to ensure compliance with the HTA's licensing standards. There appeared to be good communication between staff.

- Staff at the establishment demonstrated a sensitive approach to the use of human samples for research, including by: providing justification for the use of all human samples at the establishment; reviewing periodically the quality of the integrity of samples received; and assessing the use of human samples at the establishment.

- The establishment is developing a robust system for sample traceability and document management. The establishment has implemented an electronic document control system to strengthen document control practices.

- Staff at the establishment demonstrated that they strive towards improvement of practices, and were open to the advice offered by the HTA during the inspection.

There are a number of areas of practice that require improvement, including six minor shortfalls.

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: 01 June 2017

Report returned from DI: No comments received

Final report issued: 19 June 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: 24 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.