Site visit inspection report on compliance with HTA minimum standards

Oxford BioTherapeutics Limited

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**

2 April 2014

Summary of inspection findings

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

Although the HTA found that Oxford BioTherapeutics (the establishment) had met the majority of the HTA standards, shortfalls were found in relation to governance and quality systems and premises. The establishment does not have a formal procedure by which to evaluate potential suppliers of human tissue in order to ensure that they comply with the relevant HTA standards. Some samples of human tissue are stored in a liquid nitrogen container which is not located in a secure area. Following the inspection the establishment took steps to address the shortfalls; a procedure was put in place to evaluate suppliers of human tissue and additional steps were taken to ensure the security of the shed where samples are stored in a liquid nitrogen container.

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

The HTA's regulatory requirements

The HTA must assure itself that the Designated Individual, Licence Holder, premises and practices are suitable.

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.

The HTA developed its licensing standards with input from its stakeholders. They are designed to ensure the safe and ethical use of human tissue and the dignified and respectful treatment of the deceased. The HTA inspects the establishments it licences against four groups of standards:

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

This is an exception-based report: only those standards that have been assessed as not met are included. Where the HTA determines that a standard is not met, the level of the shortfall is classified as 'Critical', 'Major' or 'Minor' (see Appendix 2: Classification of the level of shortfall). Where HTA standards are fully met, but the HTA has identified an area of practice that could be further improved, advice is given to the DI.

Reports of HTA inspections carried out from 1 November 2010 are published on the HTA's website.

Background to the establishment and description of inspection activities undertaken

Oxford BioTherapeutics (the establishment) is an international biotechnology company, which aims to develop antibody-drug conjugates for treating cancer. It has headquarters in the UK and has a US operation in San Jose, California. The establishment is licensed by the HTA to store tissue for the scheduled purpose of research in connection with disorders, or the functioning, of the human body. The company sources human tissue from the living or the deceased; the tissues can originate from within the UK or outside the UK.

The establishment receives human tissues including excess surgical tissue. The majority of tissue is in the form of microscope slides originally used for immunohistochemical analysis. The establishment occasionally receives fresh frozen tissue, from which its scientists extract proteins and peptides in order to identify biomarkers and develop therapeutic applications for patients with various cancers.

The HTA inspected the establishment on 2 April 2014. This was the first inspection of the establishment since it was licensed in July 2009, as it was considered to be low risk.

The inspection included a visual inspection of the storage areas, review of documents and audit trail of stored samples. Interviews were held with key members of staff including the Chief Operations Officer, Associate Director of Proteomic Discovery (Designated Individual), Director of Bioinformatics (Quality Manager) and the Head of Protein Separation. Discussions were also held with the Chief Executive Officer, who is also the Corporate Licence Holder contact.

The establishment has secure access, with tissue samples stored in two laboratory areas. There are two locked freezers, each with local alarms; one freezer is kept at -80^{o}C and a back up freezer is kept at -66^{o}C. Slides containing tissues are stored at room temperature, in

locked steel cabinets. On occasion, a small amount of tissue is stored in a padlocked liquid nitrogen storage dewar located in an unlocked shed outside the building (see minor shortfall in the following section of this report). On the day of the inspection the HTA was informed that the establishment did not have any fresh frozen tissue on site.

The establishment has a range of SOPs relating to the HTA licensed activity of storage. The SOPs cover material reception, assignment of tracking codes, storing and tracking of tissues using the Laboratory Management System (LMS) computer database, packaging and shipping of tissue, reporting of adverse events, auditing of tissue samples and disposal.

The establishment has an agreement with a courier company to transport tissues. In addition, a contingency storage agreement is in place with another HTA licensed establishment in the event that tissues have to be moved out of the premises.

Tissues which arrive at the establishment are recorded on the 'sample delivery form' and assigned a unique sample code (S-number) which is used to track the sample from receipt to use or disposal. Thereafter, details including the name of supplier, tissue or cells type, original amount, current amount, preparation of sub-samples, storage location (freezer, cabinet, shelf, box and position) and research projects which the tissue is assigned to, are recorded in LMS. Transfer of tissues and disposal, if appropriate is also recorded.

Agreements between the establishment and several suppliers of human tissue, one of whom is licensed by the HTA, were reviewed during the inspection. Agreements in place with Universities in the UK and Germany were also reviewed. The establishment has stopped ordering tissues from a Chinese supplier who had previously supplied a small number of tissues. Despite its best endeavours, the establishment was not able to obtain assurances that consent in accordance with local requirements was in place for these tissues.

An audit trail was undertaken on four slides containing tissue samples, which were supplied by four different suppliers. Records were reviewed on the LMS database and slide boxes stored in the steel cabinet were checked. Disposal records relating to disposal of natural killer cells were also reviewed. These cells were disposed of as they did not meet the quality requirements for protein fractionation. No discrepancies were noted.

Inspection findings

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

Compliance with HTA standards

Governance and Quality

Standard	Inspection findings	Level of shortfall
GQ1 All aspects of the establishment's work are supported by ratified documented policies and procedures as part of the overall governance process.	The establishment receives tissues from several countries and can also receive tissues from within the UK. The establishment does not have a documented procedure to evaluate suppliers of human tissue, which ensures that suppliers meet the requirements of the HTAct and HTA Codes of Practice. There is the risk that in the absence of a formal procedure, the establishment may source tissues which do not comply with the requirements of the HT Act and HTA Codes of Practice. *Following the inspection, the establishment provided evidence that a system to evaluate suppliers of human tissue has been put in place to ensure compliance with the relevant HTA standards*.	**N/A**

Premises, Facilities and Equipment

Standard	Inspection findings	Level of shortfall
PFE3 There are appropriate facilities for the storage of bodies, body parts, tissues, cells, consumables and records.	Some tissues are stored in a small liquid nitrogen storage dewar, which is secured using a padlock but located in an unlocked shed outside the main premises. There is the risk that unauthorised persons could access the dewar and remove it or tip it over, potentially resulting in loss of any tissues stored within the container. *Following the inspection the establishment placed a lock on the shed where the liquid nitrogen storage dewar is located and undertook a risk assessment of the storage of these samples.*	**N/A**

Advice

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

No.	Standard	Advice
1.	NA	The DI is advised to display the HTA licence so that staff and visitors are aware that they work under a licence issued by the HTA.
2.	GQ1	The DI is advised to consider formal meetings with all staff, perhaps on an annual basis, to remind them of the HTA requirements.
3.	GQ8	The DI is advised to risk assess the frequency with which the liquid nitrogen level in the liquid nitrogen storage container is checked. Liquid nitrogen levels can vary depending on the ambient temperature and the number of times the storage container is accessed in order to remove samples or to place samples in storage. *Following the inspection the establishment risk assessed the storage of samples in the liquid nitrogen dewar, while taking into account monitoring and recording liquid nitrogen levels, security and contingency arrangements.*
4.	PFE 3	The establishment receives animal tissue as well as human tissue. The DI is advised to consider storing human tissue in a labelled, dedicated compartment within the -80^{o}C freezer. Some donors of human tissues may have sensitivities around storage of their tissues together with animal tissues.
5.	D1	The DI is advised to ensure that any tissues from the deceased are clearly identified so that they can be disposed of respectfully in accordance with the establishment's disposal policy.

Concluding comments

Staff at the establishment work well together as a team. There are good systems in place for record keeping and traceability; tissues are tracked from receipt to storage, use and disposal, using an overarching laboratory management system. The DI is the Assisstant Director of Proteomics and has good oversight of the HTA licensable activity.

The HTA has given advice to the Designated Individual with respect to formal meetings with staff, risk assessing the frequency of checks undertaken of nitrogen levels in the liquid nitrogen storage dewar, labelling the compartment where human tissue is stored and ensuring that tissues from the deceased are clearly identified. The HTA is satisfied that the establishment addressed two minor shortfalls identified during the inspection.

The HTA has assessed the establishment as suitable to be licensed for the activities specified.

Report sent to DI for factual accuracy: 29 April 2014

Report returned from DI: 9 May 2014

Final report issued: 22 May 2014

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
• Consent forms comply with the HTA's Code of Practice • Consent forms are in records and are made accessible to those using or releasing relevant material for a scheduled purpose • If the establishment obtains consent, a process is in place for acquiring consent in accordance with the requirements of the HT Act 2004 and the HTA's Codes of Practice • Where applicable, there are agreements with third parties to ensure that consent is obtained in accordance with the requirements of the HT Act 2004 and the HTA's Codes of Practice • Consent procedures have been ethically approved
C2 Information about the consent process is provided and in a variety of formats
• Standard operating procedures (SOPs) detail the procedure for providing information on consent • Agreements with third parties contain appropriate information • Independent interpreters are available when appropriate • Information is available in suitable formats, appropriate to the situation • Consent procedures have been ethically approved
C3 Staff involved in seeking consent receive training and support in the implications and essential requirements of taking consent
• Standard operating procedures (SOPs) detail the consent process • Evidence of suitable training of staff involved in seeking consent • Records demonstrate up-to-date staff training • Competency is assessed and maintained

Governance and quality system standards
GQ1 All aspects of the establishments work are supported by ratified documented policies and procedures as part of the overall governance process
• Policies and procedures are in place, covering all activities related to the storage of relevant material for research in connection with disorders, or the functioning, of the human body • Appropriate risk management systems are in place • Regular governance meetings are held; for example, health and safety and risk management

committees, agendas and minutes • Complaints system
GQ2 There is a documented system of quality management and audit
• A document control system, covering all documented policies and standard operating procedures (SOPs). • Schedule of audits • Change control mechanisms for the implementation of new operational procedures
GQ3 Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills
• Qualifications of staff and training are recorded, records showing attendance at training • Orientation and induction programmes • Documented training programme, (e.g. health and safety, fire, risk management, infection control), including developmental training • Training and reference manuals • Staff appraisal / review records and personal development plans are in place
GQ4 There is a systematic and planned approach to the management of records
• Documented procedures for the creation, amendment, retention and destruction of records • Regular audit of record content to check for completeness, legibility and accuracy • Back-up / recovery facility in the event of loss of records • Systems ensure data protection, confidentiality and public disclosure (whistle-blowing)
GQ5 There are documented procedures for distribution of body parts, tissues or cells
• A process is in place to review the release of relevant material to other organisations • An agreement is in place between the establishment and the organisation to whom relevant material is supplied regarding the tracking and use of material and eventual disposal or return
GQ6 A coding and records system facilitates traceability of bodies, body parts, tissues and cells, ensuring a robust audit trail
• There is an identification system which assigns a unique code to each donation and to each of the products associated with it • An audit trail is maintained, which includes details of when and where the relevant material was acquired, the consent obtained, the uses to which the material was put, when the material was transferred and to whom

GQ7 There are systems to ensure that all adverse events are investigated promptly
• Corrective and preventive actions are taken where necessary and improvements in practice are made • System to receive and distribute national and local information (e.g. HTA communications)
GQ8 Risk assessments of the establishment's practices and processes are completed regularly and are recorded and monitored appropriately
• Documented risk assessments for all practices and processes • Risk assessments are reviewed when appropriate • Staff can access risk assessments and are made aware of local hazards at training

Premises, facilities and equipment standards
PFE1 The premises are fit for purpose
• A risk assessment has been carried out of the premises to ensure that they are appropriate for the purpose • Policies in place to review and maintain the safety of staff, authorised visitors and students • The premises have sufficient space for procedures to be carried out safely and efficiently • Policies are in place to ensure that the premises are secure and confidentiality is maintained
PFE 2 Environmental controls are in place to avoid potential contamination
• Documented cleaning and decontamination procedures • Staff are provided with appropriate protective equipment and facilities that minimise risks from contamination • Appropriate health and safety controls are in place
PFE3 There are appropriate facilities for the storage of bodies, body parts, tissues and cells, consumables and records.
• Relevant material, consumables and records are stored in suitable secure environments and precautions are taken to minimise risk of damage, theft or contamination • Contingency plans are in place in case of failure in storage area • Critical storage conditions are monitored and recorded • System to deal with emergencies on 24 hour basis • Records indicating where the material is stored in the premises

PFE 4 Systems are in place to protect the quality and integrity of bodies, body parts, tissues and cells during transport and delivery to a destination

- Documented policies and procedures for the appropriate transport of relevant material, including a risk assessment of transportation
- A system is in place to ensure that traceability of relevant material is maintained during transport
- Records of transportation and delivery
- Records are kept of any agreements with recipients of relevant material
- Records are kept of any agreements with courier or transport companies

PFE5 Equipment is appropriate for use, maintained, quality assured, validated and where appropriate monitored

- Records of calibration, validation and maintenance, including any agreements with maintenance companies
- Users have access to instructions for equipment and receive training in use and maintenance where appropriate
- Staff aware of how to report an equipment problem
- Contingency plan for equipment failure

Disposal Standards

D1 There is a clear and sensitive policy for disposing of human organs and tissue

- Documented disposal policy
- Policy is made available to the public
- Compliance with health and safety recommendations

D2 The reason for disposal and the methods used are carefully documented

- Standard operating procedures (SOPs) for tracking the disposal of relevant material detail the method and reason for disposal
- Where applicable, disposal arrangements reflect specified wishes

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.