Site visit inspection report on compliance with HTA minimum standards

Quotient Bioresearch

HTA licensing number 12633

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**

17 February 2016

Summary of inspection findings

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

Although Quotient Bioresearch was found to have met the majority of HTA standards, one minor shortfall was found in respect of standard GQ7. This was in relation to incident reporting procedures.

The establishment was provided with advice and guidance about areas that could be improved further. 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 licenses 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

This report describes the first site visit inspection of Quotient Bioresearch (the establishment). The establishment has been licensed by the HTA since March 2015 for the storage of relevant material for use in research within the scope of the Human Tissue Act 2004 (HT Act). The establishment also holds an MHRA licence as it is involved in early stage specialist drug development and provides these services to companies worldwide.

The establishment receives two main tissue types: cryopreserved hepatocytes and fresh skin samples. The skin tissue is surplus material that is provided to the establishment after cosmetic surgery and is imported from Europe. The establishment receives human tissue that has consent to be used for research (see Advice, item 1). In the past, the establishment also received fresh liver tissue. The establishments also stores faeces and urine as part of ongoing clinical trials. These are held in -80^{o}C freezers and a -20^{o}C 'walk-in' freezer.

Samples are delivered by a courier to the establishment's 'Goods in' area and then collected by a member of the laboratory team, who will check that the packaging is intact and undamaged in the laboratory. The hepatocytes are transported in a liquid nitrogen dewer, which is monitored with a temperature data logger, and the skin samples are transported on dry ice. Any issues will be noted on the establishment's 'Human Tissue Usage Form'. All samples are subject to screening by the tissue providers and the establishment receives

samples that have tested negative for infectious disease markers. The hepatocytes are stored in vapour phase liquid nitrogen until they are required for an experiment. Hepatocytes are not pooled and all vials are used in a single experiment. The skin tissue is cut into sections and used in laboratory experiments. Surplus skin will be sectioned and placed on slides to be used for imaging studies.

Critical storage conditions are continuously monitored using a building management system (BMS). The system also monitors other components on the premises that require surveillance. If the temperature goes outside of normal parameters, an audible alarm will sound. The electronic software system will also alert members of staff if there is a temperature fluctuation both during and out of typical working hours. At the time of the inspection, the liquid nitrogen dewar was not being monitored by the building management system; however, a new dewar compatible with the BMS had been purchased. The laboratory manager has responsibility for monitoring the liquid nitrogen levels in the tank storing the hepatocytes. In the event that the freezer or vapour tanks fail, the establishment has on-site contingency arrangements.

The inspection included: a visual inspection of the sample processing laboratory and storage areas; a document review, and; interviews with key members of staff, including the Director of Quality Assurance, In Vitro and DDI Services Manager, Research Scientists and the Designated Individual (DI).

Four hepatocyte samples were traced from the spreadsheet and the usage forms to the storage location in the vapour phase liquid nitrogen tank. Two others were traced from their position in the tank to the paper records. There were no discrepancies noted. A skin slide stored for imaging studies was also traced from storage to the relevant records. There were no discrepancies noted.

Inspection findings

The HTA found 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
GQ7 There are systems to ensure that all adverse events are investigated promptly	Although the establishment has an adverse event procedure, it does not contain comprehensive information about dealing with incidents involving human tissue. Section 6.9 (appendix B) of the ‘Adverse Event’ SOP states that a ‘significant adverse event must be reported to the HTA Designated Individual’; however, there is no documentation to define what this is. The incident reporting procedure should be strengthened to ensure all staff	**Minor**

	working with human tissue are aware of the types of incidents that must be recorded and how these will be investigated. See Advice, item 4.	

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

No.	Standard	Advice
1.	C1	The establishment assures itself that human tissue with consent for research has been provided. A letter confirming this is held for each tissue provider. The DI may wish to consider strengthening formal agreements with each tissue provider that confirms these arrangements.
2.	GQ2	The Quality Assurance team is responsible for conducting a range of audits. Primarily, these include auditing the study files and laboratory records to ensure that all procedures have been carried out in accordance with the 'sponsor's' study plan. Where deviations are identified, corrective and preventative action plans are put in place. The current audits include elements relating to HTA matters and process audits to assess compliance with HTA standards. The DI is advised to consider developing an audit pro-forma to enable the Quality Assurance team to carry out a comprehensive audit to assess compliance with HTA standards. Furthermore, the Research Scientists also carry out inventory audits on a monthly basis. The purpose of these audits is to make sure all samples are in the correct location. The DI may wish to consider reviewing the audit information quarterly to review the types of traceability issues that are identified by the research groups. The analysis of recurring issues or evolving trends, will enable the DI to review areas that require improvement.
3.	GQ5	In other establishments, a register of 'approved suppliers' has been set up and is considered good practice. Each potential supplier is sent a 'due diligence form', asking for details of ethical approval, ethical warranties, informed consent forms, consent warranties and regulatory compliance (where appropriate). An agreement is then constructed using these criteria as the supplier's responsibilities. The DI may wish to consider adopting this practice.
4.	GQ7	The incident procedure should describe the process that staff must follow if there is an incident involving human tissue and how these will be investigated and resolved to prevent re-occurrences. Incidents may include, but are not limited to: • loss of tissue traceability (missing/incorrect documentation) • critical storage failure or temperatures outside the set ranges • loss of tissue • inappropriate disposal • security breach The DI should consider including areas of risk that are stated in the establishment's Risk Assessment Policy (POL2575). The DI may also wish to use the experience of the QA team to assist in this, since it has a well-established framework for reporting deviations from GLP and GCP.
5.	PFE5	A formal risk assessment of using portable oxygen monitors in laboratory areas where liquid nitrogen is stored, including the laboratory storing hepatocytes, has been carried out. The risk assessment covers the possible use of 'wall mounted' oxygen monitors in laboratory areas where portable

		oxygen monitors are currently being used. The DI is advised to ensure that all portable alarms are appropriately tested to ensure that they are functioning appropriately. Furthermore, the DI should also review whether the portable oxygen monitor located in the laboratory where the hepatocytes (lab 37) are stored, is correctly positioned and at the correct height to ensure that oxygen levels are detected accurately.

Concluding comments

The establishment has worked hard to achieve a high standard of compliance with the HTA standards. A number of areas of good practice were seen during the inspection:

- All staff encouraged to do the MRC e-learning, which was developed with the input of the HTA.
- Staff training files are audited regularly to ensure that staff have received training and that the content of files are identical;
- Detailed competence training for all staff is in place, which involves observation of staff carrying out procedures;
- The BMS is robust and enables the monitoring of several components, simultaneously (and remotely, at home), including temperatures, pressures, humidity levels and ventilation; it also includes data on when maintenance contracts on each piece of equipment expire.
- a risk assessment is carried out for each study in relation to the risks associated with transport, receipt, storage and disposal of human tissue.

There are some areas of practice that require improvement, including one minor shortfall against standard GQ7. The HTA has given advice to the Designated Individual on a range of issues to make further improvements.

The HTA requires that the Designated Individual addresses the shortfalls by submitting a completed corrective and preventative action (CAPA) plan 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: 11 March 2016

Report returned from DI: 11 April 2016

Final report issued: 11 April 2016

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: 22 June 2016

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.