Site visit inspection report on compliance with HTA minimum standards

Autolus Limited

HTA licensing number 12642

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**

26 January 2017

Summary of inspection findings

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

Although the HTA found that Autolus Limited (the establishment) had met the majority of the HTA standards, three minor shortfalls were found: one with regard to the Consent (C) standards and two with regard to the Governance and Quality Systems (GQS) standards. The minor shortfalls were in relation to: (i) the consent training process; (ii) internal audit; and (iii) reporting of adverse events.

Advice has been given relating to the C, GQS and Premises, Facilities and Equipment standards, as well as to licence management.

Particular examples of 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 (DI), Licence Holder (LH), premises and practices are suitable.

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.

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 refers to the activities carried out by Autolus Limited (the establishment). The establishment was issued an HTA licence in October 2015. The current inspection was the first routine site visit to assess whether the establishment is continuing to meet the HTA's standards.

Autolus Limited is a privately held biopharmaceutical company and was established in 2014. It is involved in the development of T-cell immunotherapies for the autologous treatment of both haematological and solid malignancies. The company isolates and processes cells for pre-clinical research aimed at evaluating the effectiveness of such cells in combating cancer. There are approximately 70 staff in the company.

The establishment is licensed under the Human Tissue Act 2004 (HT Act) for the storage of relevant material for use for a scheduled purpose. In this case, relevant material from living donors is being stored for the scheduled purpose of 'research in connection with disorders, or the functioning, of the human body'.

The DI supervising activities taking place under the licence is the Associate Director of Operations, the (Corporate) LH (CLH) is Autolus Limited and the CLH Contact (CLHC) is the Head of Manufacturing. There are no Persons Designated (PDs) working under the licence.

Relevant material stored under the licence is obtained from two sources: (i) consented blood donations from healthy volunteers (company employees) under the 'healthy volunteer donation programme'; and (ii) isolated cellular preparations supplied by other organisations. A

third sample set (leukapheresis buffy coat, obtained from healthy volunteers) is collected at another site, transported and stored under NHS Research Ethics Committee (REC) project-specific approval at the establishment. By virtue of this approval, this third sample set is lawfully exempted from the requirement for it to be stored under the HTA licence.

The establishment does not distribute relevant material to other organisations.

At the time of the inspection, there were 120 samples from donors stored under the licence and 30 samples from donors stored under the REC-approved project.

Healthy volunteer donation programme

If healthy volunteer donations are required, the researcher completes an 'application for donor samples' form. The 'sampling committee' (whose members make up part of the Health and Safety Committee) reviews the application. Once approved, the sampling committee informs one of two company phlebotomists and provides them with a copy of the approved application and donor consent forms.

The phlebotomist advertises for donors via email using an established list of donors (see *Advice*, item 2). At the first meeting, the phlebotomist provides the donor with a copy of the donor consent form, discusses the donation and gives the donor an opportunity to ask questions (see *Advice*, item 3). The donor returns approximately one week later to complete the consent form and undergo blood sampling.

Donor anonymity is preserved by dividing the consent form into two parts, linked by a unique donor sample (DS) number. One part is provided to the researcher, along with the sample, and the phlebotomist holds the other part securely.

Although there is a detailed and thorough consenting programme for healthy volunteers, the phlebotomists do not currently receive formalised consent training (see *Shortfall*, under C3).

Supplying organisations

Two organisations supply the establishment with freshly prepared leukocyte cones. There is an agreement with one of these suppliers (see *Advice*, items 4 and 19).

Processing

A small number of healthy volunteer donations are stored as whole blood. The remainder, along with commercially supplied leukocyte cones, are processed in the laboratory by density gradient centrifugation to isolate peripheral blood mononuclear cells (PBMCs). Cryopreservation of isolated PBMCs takes place overnight in a dedicated position within a -80°C freezer.

Storage

Cryopreserved cells are stored in one of two liquid nitrogen storage vessels (cryovessels). Whole blood is stored in a -80°C freezer although, at the time of the inspection, there were no whole blood samples being stored. There is a separate (third) -80°C freezer and surplus capacity in the cryovessels for contingency storage.

All freezers and cryovessels are linked to continuous temperature-monitoring units, which feed into an automated, wireless callout system. Temperature excursions outside the set ranges trigger both local audible alarms and the callout system but the system is not tested regularly (see *Advice*, item 16). There are no labels on the freezers or cryovessels indicating steps to be taken if the audible alarms sound (see *Advice*, item 17). There are oxygen depletion monitors in the storage room linked to an alarm system. The cryovessels are automatically filled from separate liquid nitrogen storage tanks, which are manually filled twice a week.

The inspection process

The timetable for the site visit inspection was developed after consideration of information provided at the time of licence application, compliance update information and communications with the DI. The inspection included a visual inspection of the laboratories and storage areas, discussions and interviews with key staff, and a review of documentation. Interviews were held with the DI, one Senior Scientist and a Research Scientist. Audits of traceability were also carried out.

The traceability audits were performed on six samples. These included samples from staff donors, suppliers and samples stored under the REC-approved project (two from each group). The samples were randomly selected from the electronic tissue register and then located in the cryovessels. Sample labelling details were compared to the electronic records. Although there was traceability for all of the samples, minor discrepancies in the traceability records were identified:

- The establishment's procedure requires that all samples be labelled with the DS number. If multiple samples are created from the primary sample, a linked secondary numbering system is used. Two samples from staff donors showed inconsistency in this labelling practice (see *Advice*, item 13).
- The storage rack details for two samples from suppliers were incorrectly recorded on the register. In addition, the rack containing these samples had been moved to the other cryovessel and this had not been recorded.
- For the two samples stored under the REC-approved project, the number of sample vials exceeded the number of vial spaces allocated on the register, and these extra samples were found to be randomly located (see *Advice*, item 14).

Consent forms were reviewed for the two samples from staff donors. Minor discrepancies were identified in one of these, where the form had been signed and dated by the donor at the end, but each of the consent statements had not been initialled by the donor (see *Advice*, item 3).

Inspection findings

The HTA found the DI and the CLH to be suitable in accordance with the requirements of the legislation.

Compliance with HTA standards

Consent

Standard	Inspection findings	Level of shortfall
C3 Staff involved in seeking consent receive training and support in the implications and essential requirements of taking consent.	There is no formalised consent training process for phlebotomists involved in seeking consent from staff donors. See *Advice*, item 6.	**Minor**

Governance and Quality

Standard	Inspection findings	Level of shortfall
GQ2 There is a documented system of quality management and audit.	Some scientists have carried out *ad hoc* stock checks on selected sample sets whereas others have not. A shortfall in audits was identified during the licence application assessment. An audit template was developed as a result of this but this has not been adopted. The HTA inspection audit revealed discrepancies in some of the human tissue sample sets, which might have been otherwise picked up if audits had been taking place. See *Advice*, item 10.	**Minor**
GQ7 There are systems to ensure that all adverse events are investigated promptly.	The recording of adverse events relating to human tissue is on an *ad hoc* basis. A shortfall in identifying, recording and reporting adverse events was identified during the licence application assessment. A document was developed as a result of this but this has not been adopted.	**Minor**

Advice

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

No.	Standard	Advice
1.	N/A	The DI is advised to consider appointing a PD to assist him in the role; the HTA should be notified of such an appointment.
2.	C1	The current practice is that the email to staff donors is visible to all volunteer donors on the list. To support anonymity, the DI is advised to consider how this could be improved.
3.	C1	The procedure for seeking consent is currently included in the Quality Manual (POL-0008: 'Approval and collection of donor samples for laboratory research'). The DI is advised to consider whether this could be a separate SOP as part of the Quality Management System. The DI is advised to consider updating the consent procedure to ensure that consent forms are checked for accuracy and completeness by the phlebotomist once completed by the donor.
4.	C1	To improve current assurances with respect to supplied samples, the DI is advised to consider putting in place an agreement with the second supplier, which ensures that the samples have been donated with appropriate and valid consent.
5.	C2	The research undertaken could give rise to clinically significant results or incidental findings. The DI is advised to consider including information about

		health related findings in the donor information sheet and as part of the phlebotomist's discussion with the donor. Information about health related findings in research can be found in the following document: https://www.mrc.ac.uk/documents/pdf/mrc-wellcome-trust-framework-on-the-feedback-of-health-related-findings-in-researchpdf/
6.	C3	Components of the consent training process could include the HTA Code of Practice on Consent (Code 1) and the presentation created by the DI ('Obtaining valid consent'). The DI is also advised to consider refresher training for phlebotomists after an appropriate time.
7.	GQ1	The Quality Manual (POL-0008) is wide ranging and includes several procedures and risk assessments. It would be more appropriate to include these as separate, 'stand-alone' documents (e.g. procedures on consent, audit, adverse events and disposal).
8.	GQ1	Governance matters relating to licensed activities are an agenda item of Health and Safety Committee meetings. Given the wide-ranging agenda of this Committee, and in the context of the identified shortfalls, separate regular governance meetings where the DI, CLHC and other staff can discuss governance matters would help to strengthen governance arrangements.
9.	GQ1	During the inspection, discrepancies in certain documents were noted: - The presentation ('Obtaining valid consent'), used as part of consent training, is not linked to a document number or version. - POL-0009: 'In-lab controlled temperature storage' does not include the set temperature ranges for -80°C freezers. The DI is advised to consider including an audit of the accuracy of documents as part of the audit schedule.
10.	GQ2	The DI has already created a detailed audit template (FRM-0003: 'Human tissue audit form'), which covers horizontal audits, to ensure that SOPs accurately reflect current practices, and vertical traceability audits, from records of consent and receipt to storage, use, distribution or disposal. No audits have yet been conducted using this form. The DI may also wish to consider including a regular audit against HTA standards as part of the audit schedule.
11.	GQ3	To strengthen existing training arrangements, the DI is advised to consider how competency can be assessed and maintained.
12.	GQ3	The DI may wish to consider including online training packages as part of the staff training programme. One example is the MRC 'Research and Human Tissue Legislation e-learning Module', part of the MRC Data and Tissues Toolkit (both of which were developed with input from the HTA): http://byglearning.co.uk/mrcrsc-lms/course/category.php?id=1
13.	GQ4	There is documentation for the creation of primary sample labels (DS numbers). The DI is advised to consider formalising the system for creating secondary, linked sample labels.

14.	GQ6	The DI is advised to consider the following to strengthen sample traceability: - A modification of the consent form (FRM-0001: 'Donor consent form') so that it is clear which phlebotomist has obtained donor consent. - A more accurate and robust way of recording sample location.
15.	GQ8	The DI is advised to ensure that risk assessments are reviewed regularly.
16.	PFE3	The DI is advised to consider regular testing of the temperature alarm callout system to ensure that it is functioning correctly.
17.	PFE3	The DI is advised to consider placing labels on freezers and cryovessels to summarise procedures to take when the audible temperature alarms are activated.
18.	PFE3	The DI is advised to consider highlighting freezers and cryovessels that contain human tissue to prevent sample mix-ups and to ensure that staff are aware of the need to manage such samples in line with the regulatory requirements.
19.	PFE4	To improve current assurances with respect to supplied samples, the DI is advised to consider putting in place an agreement with the second supplier, which covers: sample traceability; transport conditions; and the reporting of relevant adverse events relating to transport.

Concluding comments

During the inspection, two areas of good practice were noted:

- There is a detailed process for obtaining consent, which includes steps to ensure donor anonymity, informed consent, a time for donors to change their mind and an opportunity to withdraw consent at any time.
- The establishment uses two databases, one to record sample details and one to record sample location. These systems can be cross-referenced using the DS number.

There are a number of areas of practice that require improvement, including three minor shortfalls. The HTA has given advice to the DI with respect to the Consent, Governance and Quality Systems and Premises, Facilities and Equipment standards, as well as to licence management.

The HTA requires that the DI 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: 22 February 2017

Report returned from DI: 14 March 2017

Final report issued: 20 April 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: 18 May 2018

Appendix 1: HTA standards

The HTA standards applicable to this establishment are shown below. Individual standards that 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)
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 that 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 either which will usually be assessed by the HTA by desk based or site visit inspection.

   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.