Site visit inspection report on compliance with HTA minimum standards

LGC Ltd

HTA licensing number 12609

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**

9 September 2014

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 LGC Ltd (the establishment) had met the majority of the HTA standards, three minor shortfalls were found with regard to the Consent (C) and Governance and Quality Systems (GQS) standards. The shortfalls were in relation to consent practices for volunteer donations and governance meetings. Advice has also been given relating to the C, GQS, Premises, Facilities and Equipment (PFE) and Disposal (D) standards.

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 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

This report refers to the activities carried out by LGC Ltd (the establishment). This was the first site visit inspection of the establishment since it was issued an HTA licence in August 2013. It was a routine site visit inspection to assess whether the establishment is meeting the HTA's standards.

LGC was founded originally as the Laboratory for the Government Chemist in 1842. There are 13 divisions of LGC in the UK and these focus on laboratory services, measurement standards, genomics, reference materials and proficiency testing. Two of the Divisions are licensed by the HTA for the storage of relevant material for research: LGC Genomics (HTA licence number 12600) and LGC Ltd (the establishment; HTA licence number 12609). LGC Ltd has approximately 245 employees. The establishment is a Contract Research Organisation (CRO), providing a service to research programmes of both sponsors and customers in the pharmaceutical and biotechnology industries. Some of these studies involve analyses of samples derived from clinical trials. While the trial lasts, the study is under United Kingdom Ethics Committee Authority (UKECA) approval and the storage of such relevant material is exempt from the HTA's licensing arrangements. These trials are conducted in compliance with Good Laboratory Practice (GLP) and Good Clinical Practice (GCP) and the conduct of the trial is subject to inspection by the Medicines and Healthcare Products Regulatory Agency (MHRA). However, any samples which are retained following completion of the trial fall under the HTA licence.

The Quality Assurance (QA) Department within the organisation is involved in the regular audit of all contract research studies, including those involving clinical trials (see below).

Relevant material (from living donors) is stored for the scheduled purposes of: (i) research in connection with disorders, or the functioning, of the human body ('research'), and; (ii) performance assessment.

Research activity at LGC Ltd is centred on *in vitro* drug metabolism pharmacokinetic (DMPK) studies. Samples stored for research under the HTA licence include: non-clinical trial samples involved in a study for a sponsor or customer; samples previously part of a clinical trial; those received from tissue suppliers (see below), and; healthy volunteer donations from members of staff.

The preparation of calibration standards has been interpreted by the establishment as being the scheduled purpose of 'performance assessment'.

The establishment stores over 10,000 normal and diseased human samples. These include isolated cellular preparations (kidney cells), body fluid specimens (sputum and saliva swabs), dried blood spot (DBS) cards, plasma and urine samples.

Tissue sources: Consent and ethical approval

Tissue is supplied to LGC from sources both within and outside the U.K. Suppliers of human tissue include commercial organisations, NHS Trusts, universities and Research Tissue Banks (RTBs). Each supplier completes a GCP Compliance Statement, giving assurances that informed consent has been sought and regulatory and ethical committee approval have been obtained. A Material Transfer Agreement (MTA) is then drawn up with each organisation. The tissue supplier will arrange transportation.

Healthy volunteers are recruited from within the workforce at LGC. Samples donated include blood and urine. Blood samples are procured by any one of nine trained staff phlebotomists. Urine samples are given directly by staff volunteers to the laboratory.

Sample storage

There are three storage areas within the establishment – the interim storage area, the sample management storage area and the long-term storage area.

Human tissue samples which are received into the establishment are logged onto paper 'sample handling forms' and into an electronic Laboratory Information Management System (LIMS), which is backed up. The sample handling form acts as a chain of custody document and accompanies the sample at all times. Tissue samples are allocated a unique LGC number referring to the particular study or project (*see Advice item 9*). The samples are stored in the interim storage area, which contains one -20°C freezer and one refrigerator. The samples are then transferred to the sample management storage area, containing one -20°C freezer and one -80°C freezer, as well as a cupboard for ambient temperature storage. In this area there is an integrity check of the samples and checking of the labels. Non-conforming samples are quarantined. Conforming samples are transferred to the long-term storage area, which contains twenty-three -80°C freezers, one 'walk-in' -20°C freezer and two other -20°C freezers.

All storage areas, refrigerators and freezers are linked to a data-logged, continuous temperature and humidity monitoring facility which feeds into a wireless callout system. Excursions outside the set ranges trigger both audible alarms and the wireless callout system. Power failure to the storage facilities also triggers the audible alarms and the wireless callout system (*see Advice item 10*).

Emergency backup refrigerators and freezers are available in the event of storage failure.

Sample transport and distribution

The establishment occasionally distributes tissue to other sites or returns samples to the sponsor. Sponsors arrange the shipment of such samples.

The site visit inspection included a visual inspection of the laboratories and the storage facilities for tissue and records. Meetings were held with the DI (Health, Safety and Environmental Coordinator), two Persons Designated (PDs; Associate Director – Biologicals and GLP Facility Manager; and, Senior Laboratory Support Technician), the Principal Quality Assurance Advisor and the Quality Project Manager. A documentation review and vertical and horizontal audits were carried out. Details of the three separate audits are provided below.

In the interim storage area, one batch of samples was selected at random from the -20°C freezer. The location details were compared to the paper records for delivery and traceability. No anomalies were found.

In the sample management area, one batch of samples was selected that was undergoing the sample receipt process and so was tracked using the paper based record system. The location details were compared to the paper records for delivery and sample tracking. No anomalies were found.

In the long-term storage area, four batches of samples were selected at random from three different freezers. The sample details and locations were compared to the electronic database. No anomalies were found in the freezer locations detailed for the cryoboxes containing these batches of samples. However, there were discrepancies in the number of samples within the batch found for two of batches included in the audit. One batch of samples contained one additional sample that was not recorded on the electronic database. Another batch of samples contained three fewer samples than were recorded on the electronic database. Advice has been given to the establishment to consider strengthening the unique identification system used to provide traceability of samples (*see Advice item 9*).

Inspection findings

The HTA found the DI and the (Corporate) LH (CLH) 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 Code of Practice.	There is no formal procedure for obtaining consenting from staff donors for the collection of blood and urine samples in accordance with the HTA's Code of Practice on Consent (Code 1). *See Advice items 1 and 4*.	**Minor**
C3 Staff involved in seeking consent receive training and support in the implications and essential requirements of taking consent.	There is no formal training for staff in the seeking of consent for blood and urine donations. *See Advice items 3 and 4*.	**Minor**

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.	There are no existing regular governance meetings which cover HTA issues for staff working under the licence. *See Advice item 5*.	**Minor**

Advice

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

No.	Standard	Advice
1.	C1	The Health Research Authority (HRA) has produced a series of consent templates. The DI may wish to consider using the consent form template when creating a new consent form: http://www.hra-decisiontools.org.uk/consent/examples.html
2.	C2	The donor information sheets provided by the establishment for blood and urine donations are general in their description of the use of donated samples. The DI is advised to consider revising the information available to ensure that donors are fully informed of the specific uses to which their samples may be put. In particular, the revised information sheets should consider the following: - Donors are made aware that samples will be fully anonymised so there will be no link between donor and sample. - Donors are adequately informed that they may be asked to donate repeatedly due to their biological characteristics (if this applies). The DI should note that lifestyle or medical history may have changed since the last donation. - Donors should be asked about whether they wish to be informed about any underlying medical conditions identified through the research analysis. Further information about health related findings in research is given in the following document: http://www.wellcome.ac.uk/stellent/groups/corporatesite/@policy_communications/documents/web_document/wtp056059.pdf The DI may wish to consider using the HRA participant information sheet template when creating a new donor information sheet: http://www.hra-decisiontools.org.uk/consent/examples.html The provision of information, including the donor exclusion criteria, prior to the discussion where consent is sought will also allow the potential donor the opportunity to decline the donation without any further questions being asked.

3.	C3	The DI may wish to consider including the HTA Code of Practice on Consent (Code 1) and the Elearning package provided by the Clinical Research Network of the National Institute of Health Research when devising a consent training course. The DI is advised also to implement and document refresher training in consent for relevant staff to ensure that they are up to date in their knowledge.
4.	C1-C3	The DI is advised to ensure that the consent procedure, consent forms, participant information sheets and consent training are reviewed by the LGC Bioethics Committee.
5.	GQ1	In other establishments, regular governance meetings have covered items such as: adverse incidents, changes to Standard Operating Procedures (SOPs), audits and their findings, risk assessments, HTA training, the setting up of agreements with other establishments and updates from the HTA (e.g. e-newsletter items). It is advised that these meetings should be governed by an agenda, and minutes circulated. The minutes should include timelines for identified actions and there should be a standing agenda item for discussing progress against actions identified at previous meetings.
6.	GQ1	The DI may wish to consider setting up meetings with other DIs working both within and outside the organisation, to share information and experience with them and their PDs. This may help facilitate learning and understanding of staff at the establishment as well as being a forum for the discussion of good practices.
7.	GQ2	The DI is advised to expand the scope of the current audit schedule to include samples obtained from staff donations. These audits should include the blood and urine samples in storage and the completion of consent documentation for these samples.
8.	GQ3	The establishment maintains comprehensive training files for members of staff, including details of completion of HTA specific training. The DI is advised to periodically review the completion of staff training files to ensure that they have been completed correctly and that all staff involved in licensable activities have completed the HTA training. The DI may wish to consider including 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), as part of the staff training programme: http://www.rsclearn.mrc.ac.uk/
9.	GQ6	The establishment currently traces samples by assigning a LGC unique identification number to each batch of samples and tracking the number of samples within each batch on the cryobox label for each batch and on the electronic database. The DI is advised to consider strengthening this system to ensure that the number of samples within each batch is updated on the cryobox label. This may address the occurrence of anomalies in traceability, such as those identified in the HTA's audit trail.

10.	PFE3	Although the establishment's storage areas and refrigerator and freezer system are alarmed and temperature monitored, the establishment does not review the recorded temperature plots. The DI is advised to initiate a program by which, at suitable timeframes, the temperature plots from the monitoring system are reviewed. This may help to identify a potential failure of the system before it occurs. The DI is also advised to carry out regular testing of the tissue storage alarm system to ensure that the callout procedure is functioning correctly.
11.	PFE3	The DI is advised to ensure that storage facilities which contain human tissue are appropriately labelled to indicate this.
12.	PFE3	The DI is advised to review the storage of completed consent forms for staff donations. This may include a secure storage area for staff to deposit their completed consent form and centralised long-term storage of all completed consent forms. These measures will help to ensure that donor confidentiality is maintained and that completed consent forms are available for audit purposes (*see Advice item 7*). This applies to forms for both blood and urine donations.
13.	PFE5	The DI is advised to ensure that the refrigerators and freezers containing human tissue are decontaminated and cleaned on a regular basis and that this is recorded.
14.	D2	The DI is advised to ensure that the reason for disposal of each tissue sample is recorded and that the necessity for recording the reason is included in the relevant SOP.

Concluding comments

During the site visit inspection of the establishment several areas of good practice were noted:

- There is a robust system in place to document the chain of custody of samples delivered to the site which records the movement of samples from receipt through to the sample handling team. This sample receipt and handling record ensures that all samples received on site are handled, accounted for and appropriately logged on the establishment's LIMS.
- The establishment is well supported by the QA Department which has a robust approach to document control, incident management and audits.

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, Premises, Facilities and Equipment and Disposal standards.

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: 7 October 2014

Report returned from DI: 17 October 2014

Final report issued: 12 November 2014

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: 1 December 2015

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
PFE2 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

PFE4 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.