Site visit inspection report on compliance with HTA licensing standards

UCB Celltech

HTA licensing number 12504

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**

01 March 2018

Summary of inspection findings

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

Although the HTA found that UCB Celltech had met the majority of the HTA's standards, one major shortfall was found against the Traceability standards, and five minor shortfalls were identified against Consent, Governance and quality systems and Traceability standards.

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

The HTA's regulatory requirements

Prior to the grant of a licence, the HTA must assure itself that the Designated Individual is a suitable person to supervise the activity authorised by the licence and that the premises are suitable for the activity.

The statutory duties of the Designated Individual are set down in Section 18 of the Human Tissue Act 2004. They are to secure that:

- the other persons to whom the licence applies are suitable persons to participate in the carrying-on of the licensed activity;
- suitable practices are used in the course of carrying on that activity; and
- the conditions of the licence are complied with.

Its programme of site visit inspections to assess compliance with HTA licensing standards is one of the assurance mechanisms used by the HTA.

The HTA developed its licensing standards with input from its stakeholders. They are designed to ensure the safe and ethical use of human tissue and the dignified and respectful treatment of the deceased. They are grouped under four headings:

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

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

HTA inspection reports are published on the HTA's website.

Background to the establishment

UCB Celltech is a branch of UCB Pharma S.A., a global pharmaceutical company with a focus on neurology and immunology. The DI is a Senior Principle Scientist and the Corporate Licence Holder contact is Head of Discovery Research. This report refers to the activities carried out by UCB Celltech (the establishment), based in Slough, Berkshire. This was the second site visit inspection of the establishment, the last one being in June 2012. It was a routine inspection to assess whether the establishment is meeting the HTA's standards.

Tissue sources

Relevant material is supplied to UCB Celltech from commercial suppliers and collaborators, both within and outside the UK. Each supplier is asked to give assurance that informed consent has been sought. The establishment works with a range of biological material including, but not limited to, tumour tissue, skin, brain, kidney, liver, serum, plasma and whole blood. Material may be from the living or the deceased. The establishment stores frozen tissue, formalin fixed paraffin embedded tissue in blocks and slides and disaggregated cells/suspensions.

Blood samples, collected from healthy volunteers recruited from within the workforce at UCB Celltech, are taken by trained Occupational Health staff phlebotomists. Before each donation consent is obtained, once the donor has read the participant information sheet and the eligibility checklist. Donors sign to re-confirm their consent every time they donate. Blood samples are collected for targeted studies on request of internal investigators. The healthy volunteer donations are anonymised by utilising a sample code based on the date of collection and appointment slot the donor is given. How the code is used is clearly described to all donors by way of a poster in the phlebotomy room.

Sample storage

Human tissue samples, from outside the organisation, are received into the stores department where the barcode on the accompanying documentation is scanned. This forms part of the chain-of-custody documentation and the scientist collecting the samples signs electronically when collecting the samples from the stores area. Samples are not retained within the stores area but are collected by the requesting scientist. If necessary, staff in the stores department will top up dry ice levels. Occasionally deliveries may be received by the security staff out of hours. Any out of hours deliveries are transferred to stores the following morning where they are scanned into the tracking system (see *Advice,* item 3).

The establishment stores samples in the manner most appropriate for the specific sample type. There are two -80°C freezers dedicated for the storage of human tissue, both are locked using a combination lock, and clearly labelled. There is a liquid nitrogen dewar solely for the storage of human samples, which is locked. The access codes to all the locks for the freezers and the dewar are regularly changed to ensure a limited staff group has access to tissue. There is back up storage capacity for both the -80°C freezer and the liquid nitrogen dewar in case of equipment failure. Individual storage units are labelled with the name and contact details of the scientist responsible for that unit and the samples it contains.

There are a number of cold rooms throughout the building, two of which contain locked boxes for human tissue samples. All the fridges and freezers are connected to a central monitoring and alarm system, which is regularly tested. There are a large number of tissue blocks and slides stored at room temperature.

Traceability of human tissue within UCB Celltech

All tissue, with the exception of slides, is tracked through the establishment's 'item tracker' system. However, there is no consistency across the samples as to how they are recorded or labelled. There is the facility to print labels for samples, but this is not always used and some of the hand written labels are easy to misread. A number of the samples reviewed did not reflect the labeling convention described in the establishment's SOP (see shortfall T1(a)). As some scientists handwrite sample details, aliquots are not given there own unique reference, the rationale for this being that there isn't enough space on the vial. While the sample tracking system does assign a unique ID for each sample, this ID is assigned after the sample has been labelled and stored, when it is logged into the tracking system (see *Advice,* item 2)

The tissue tracking system does not have the facility to record when tissue is disposed of; it records only who has removed the sample from storage. When tissue is used or disposed of as part of research, this is recorded in the individual investigator's electronic study notebook, enabling the establishment to trace the fate of those samples. However, this does not take in to account those cases where tissue is disposed of outside of a research project, such as when a donor withdraws consent. A newly introduced process will now record these cases as an incident and record details of how, when and by whom tissue is disposed. However this is not linked to the tissue log in item tracker and it could therefore be difficult to find the specific incident related to the removal of the tissue (see shortfall against standard T2(b)).

Description of inspection activities undertaken

The inspection timetable was developed after consideration of the establishment's previous inspection report, compliance update information and communications with the HTA. The site visit inspection included a visual inspection of the laboratories and the storage facilities for tissue, a documentation review and horizontal audits of tissue in storage. There was a roundtable discussion with the DI, the Head of Preclinical Quality and the Head of Translational Biology was held.

Traceability audits were performed on 19 samples comprising; six samples in -80°C storage, two samples in LN2 storage, four samples stored in boxes in cold rooms, and three paraffin embedded blocks and four slides stored at room temperature. Of the six samples randomly selected from the LN2 dewar, one was an original vial labelled by an external supplier. The remaining five samples had handwritten labels and were all human stellate cells. No vials had a unique identifier and two were labelled with a date that did not match the details logged in the sample tracking system. On investigation, it was noted that the samples were the correct cell type but while they had been logged against the DI's name they were likely to have been logged by a junior member of staff, which questions the reliability of the data on the item tracker system (see shortfall against T1 (b)).

Two tissue pieces, a breast tumour from the deceased and nasal polyp from a healthy donor, were randomly selected from the tracking system and traced to their location in the -80°C freezers with no anomalies being identified. Additionally, two vials of commercially available peripheral blood mononuclear cell (PBMC) control samples and two sets of slides were traced to their respective locations in the 4ºC cold rooms, again with no anomalies being identified.

Three paraffin embedded blocks (comprising samples from the living and the deceased) and four slides stored at room temperature were randomly selected and traced back to experimental records and supplier invoices. Blocks were stored separately, but adjacent to

animal tissue blocks. However, slides were identified by experimental protocol and were mixed with animal control tissue. At the time of inspection, the lead histopathology scientist was absent and staff at the establishment had difficulty differentiating human slides from animal, or locating all associated documentation (see shortfall against T1 (b)).

Inspection findings

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

Compliance with HTA standards

Consent

Standard	Inspection findings	Level of shortfall
C1 Consent is obtained in accordance with the requirements of the Human Tissue Act 2004 (HT Act) and as set out in the HTA's Codes of Practice		
a) Consent procedures are documented and these, along with any associated documents, comply with the HT Act and the HTA's Codes of Practice.	The 'HTA Policy and Procedures' document in place at the time of inspection stated that, the donor of external, anonymised tissue withdraws consent, their samples in storage do not need to be sent for disposal. During the inspection, a draft SOP that correctly confirms that samples should be disposed of if consent withdrawn, was available to view. However, document has not been issued to staff and the practice of retaining samples when consent is withdrawn is still in place. The consent form signed by internal donors states that upon request, samples in storage would be destroyed. However, where donors have in the past asked to be removed from the donor list, it was not confirmed whether or not they also wanted their samples destroyed. This leaves the potential risk that donors forget that they need to separately request to dispose of samples when they withdraw from the donor pool (See Advice, item 1).	**Minor**
C2 Staff involved in seeking consent receive training and support in the essential requirements of taking consent		

a) There is suitable training and support of staff involved in seeking consent, which addresses the requirements of the HT Act and the HTA's Codes of Practice.	The refresher consent training given to staff states that if tissue samples are 'existing holdings' then a licence is not required. This is not the case; a licence for storage is required but as the HT Act's requirements with regards to consent are not retrospective, the HT Act's consent requirements do not apply.	**Minor**

Governance and Quality

Standard	**Inspection findings**	**Level of shortfall**
GQ4 There is a systematic and planned approach to the management of records		
c) Systems ensure data protection, confidentiality and public disclosure (whistleblowing).	The internal blood donation diary is kept in a public place visible to any staff member wishing to check who has donated. Because the coding system for donors is the date and donation slot, staff could easily track a blood sample back to an identifiable donor. This practice means that donor confidentiality may be compromised.	**Minor**

Traceability

Standard	**Inspection findings**	**Level of shortfall**
T1 A coding and records system facilitates the traceability of bodies and human tissue, ensuring a robust audit trail		

b) A register of donated material, and the associated products where relevant, is maintained.	While the establishment does have a documented coding convention this is not followed by all staff and sample products (aliquots and slides) are not given a unique code (See *Advice*, item 3). A review of slides for individual immunohistological experimentation identified sets containing a mix of human, murine and non-human primate tissue stored together. It was not possible to identify the tissue donor species, the type of tissue or original block for a number of slides reviewed during the traceability audit. During the inspection it was noted that, on one occasion, a 'card' box containing samples in the LN2 dewars had disintegrated releasing its contents. All samples were recovered but boxes audited during the inspection contained multiple sets of hepatic stellate cells which had not been labelled following the convention specified in establishment SOPs. This leads to the potential risk of misidentifying the samples when they were placed back into storage.	**Major**
c) An audit trail is maintained, which includes details of: when and where the bodies or tissue were acquired and received; the consent obtained; all sample storage locations; the uses to which any material was put; when and where the material was transferred, and to whom.	There is an audit trail of samples logged into the sample tracking system that accounts for all relevant material in storage. This system is completed by the staff member placing the individual samples into storage and is logged against their name, through the use of a secure password. During the traceability audit, inconsistencies were identified on several sample vials that had been recorded as being logged by the DI. Upon investigation, the establishment thought they could confirm the identity of the individual samples, as they had been labelled on the vial by a temporary member of staff on a particular date. Traceability records for the slides stored at room temperature are maintained on an excel spreadsheet rather than the electronic database used for all other sample types. At the time of inspection, staff were unable to consistently identify slides containing relevant material as they were mixed in with non human tissue slides and had been labelled as per experimental protocol and did not include any traceable tissue identifiers.	**Minor**

T2 Bodies and human tissue are disposed of in an appropriate manner		
b) The date, reason for disposal and the method used are documented.	Disposal of samples removed from the tracking system for experimental purposes can only be traced by searching through the electronic laboratory books of establishment staff who removed the tissue from storage. At the time of inspection, any tissue disposed of outside of a research study had not been recorded. The establishment stated that a new process had been put in place, whereby any samples disposed of outside of research would be recorded as an incident. However, this system does not connect with the tracking software and there isn't a link to allow an audit of this process. New tracking software, currently undergoing validation, should address this issue.	**Minor**

Advice

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

No.	Standard	Advice
1.	C1(a)	The DI is advised to audit samples where consent was withdrawn to ensure that the sample has been correctly disposed of.
2.	PFE1(b)	The boxes storing relevant material at 4°C are locked with a key that is kept on the desk of the individual responsible for the study, and accessed by others when needed. The DI is advised to introduce a register to sign the key in and out so there is a record of when it was used and by whom.
3.	T1 (d)	Deliveries are received into the stores department. On receipt, deliveries including relevant material, are scanned into the establishment's database and a notification is sent to the requesting scientist, who will arrange collection of the material. Relevant material is not stored on receipt, although stores staff will top up dry ice levels if necessary. Occasionally, deliveries will arrive out of hours and be received by security staff and held at main reception. These deliveries are transferred to the stores department and scanned into the establishment's database the following morning. The DI is advised to risk assess this process and implement any mitigating actions identified as necessary to limit any risks to the integrity of relevant material received in this way, and the associated traceability of the samples (chain of custody).
4.	T1(b)	The current sample tracking system assigns a unique ID to each sample recorded in the system. This unique ID is currently assigned to samples when they are logged into the system after the sample has been labelled and placed

		into storage, rather than prior to labelling. This means that not all samples stored at the establishment are labelled with the unique ID. The DI is advised to consider implementing a tracking system where samples, including aliquots, are assigned a unique ID and then labelled with that ID to facilitate tracking throughout the product lifecycle.
5.	N/A	On inspection it was noted that the ethical approval for procurement and use of NHSBT sourced blood cones is as a Research Tissue Bank (RTB); however, the establishment stated that they are not operating in that capacity. On initial application for approval the establishment were informed they needed to apply as a Research Tissue Bank (RTB) in order to be able to receive generic ethical approval for a wide range of related studies, rather then receiving approval for individual studies. The samples therefore are also under the HTA's remit and as such the samples could be reviewed during the next HTA inspection. The DI is advised to liaise with the relevant Research Ethics Committee to assure themselves that their ethical approval remains appropriate for their activities and there is sufficient ethical oversight.

Concluding comments

There were areas of good practice at the establishment, where the integrity of tissue is paramount and maintenance of equipment is to a high standard. Frequent changing of the codes for the combination locks for fridges, freezers and dewars helps to provide assurance that only appropriate staff have access to human tissue. Signage is well used in the storage areas with the name and contact details of the lead scientist to be informed if there were any problems or equipment malfunctions.

There are a number of areas of practice that require improvement, including one major and five minor shortfalls.

The HTA requires the Designated Individual to submit a completed corrective and preventative action (CAPA) plan setting out how the shortfalls will be addressed, within 14 days of receipt of the final report (refer to Appendix 2 for recommended timeframes within which to complete actions). The HTA will then inform the establishment of the evidence required to demonstrate that the actions agreed in the plan have been completed.

The HTA has assessed the establishment as suitable to be licensed for the activities specified subject to corrective and preventative actions being implemented to meet the shortfalls identified during the inspection.

Report sent to DI for factual accuracy: 29 March 2018

Report returned from DI: 13 April 2018

Final report issued: 03 May 2018

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: 28 December 2018

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
a) Consent procedures are documented and these, along with any associated documents, comply with the HT Act and the HTA's Codes of Practice. b) Consent forms are available to those using or releasing relevant material for a scheduled purpose. c) Where applicable, there are agreements with other parties to ensure that consent is obtained in accordance with the requirements of the HT Act and the HTA's Codes of Practice. d) Written information is provided to those from whom consent is sought, which reflects the requirements of the HT Act and the HTA's Codes of Practice. e) Language translations are available when appropriate. f) Information is available in formats appropriate to the situation.
C2 Staff involved in seeking consent receive training and support in the essential requirements of taking consent
a) There is suitable training and support of staff involved in seeking consent, which addresses the requirements of the HT Act and the HTA's Codes of Practice. b) Records demonstrate up-to-date staff training. c) Competency is assessed and maintained.

Governance and quality system standards
GQ1 All aspects of the establishments work are governed by documented policies and procedures as part of the overall governance process
a) Ratified, documented and up-to-date policies and procedures are in place, covering all licensable activities. b) There is a document control system. c) There are change control mechanisms for the implementation of new operational procedures. d) Matters relating to HTA-licensed activities are discussed at regular governance meetings, involving establishment staff. e) There is a system for managing complaints.
GQ2 There is a documented system of audit
a) There is a documented schedule of audits covering licensable activities. b) Audit findings include who is responsible for follow-up actions and the timeframes for completing these.
GQ3 Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills
a) Qualifications of staff and all training are recorded, records showing attendance at training. b) There are documented induction training programmes for new staff. c) Training provisions include those for visiting staff. d) Staff have appraisals and personal development plans.
GQ4 There is a systematic and planned approach to the management of records
a) There are suitable systems for the creation, review, amendment, retention and destruction of records. b) There are provisions for back-up / recovery in the event of loss of records. c) Systems ensure data protection, confidentiality and public disclosure (whistleblowing).
GQ5 There are systems to ensure that all adverse events are investigated promptly
a) Staff are instructed in how to use incident reporting systems. b) Effective corrective and preventive actions are taken where necessary and improvements in practice are made.
GQ6 Risk assessments of the establishment's practices and processes are completed regularly, recorded and monitored
a) There are documented risk assessments for all practices and processes requiring compliance with the HT Act and the HTA's Codes of Practice. b) Risk assessments are reviewed regularly.

c) Staff can access risk assessments and are made aware of risks during training.

Traceability standards
T1 A coding and records system facilitates the traceability of bodies and human tissue, ensuring a robust audit trail
a) There is an identification system which assigns a unique code to each donation and to each of the products associated with it. b) A register of donated material and the associated products where relevant, is maintained. c) An audit trail is maintained, which includes details of: when and where the bodies or tissue were acquired and received; the consent obtained; all sample storage locations; the uses to which any material was put; when and where the material was transferred, and to whom. d) A system is in place to ensure that traceability of relevant material is maintained during transport. e) Records of transportation and delivery are kept. f) Records of any agreements with courier or transport companies are kept. g) Records of any agreements with recipients of relevant material are kept.
T2 Bodies and human tissue are disposed of in an appropriate manner
a) Disposal is carried out in accordance with the HTA's Codes of Practice. b) The date, reason for disposal and the method used are documented.

Premises, facilities and equipment standards
PFE1 The premises are secure and fit for purpose
a) An assessment of the premises has been carried out to ensure that they are appropriate for the purpose. b) Arrangements are in place to ensure that the premises are secure and confidentiality is maintained. c) There are documented cleaning and decontamination procedures.
PFE2 There are appropriate facilities for the storage of bodies and human tissue
a) There is sufficient storage capacity. b) Where relevant, storage arrangements ensure the dignity of the deceased. c) Storage conditions are monitored, recorded and acted on when required. d) There are documented contingency plans in place in case of failure in storage area.

PFE3 Equipment is appropriate for use, maintained, validated and where appropriate monitored
a) Equipment is subject to recommended calibration, validation, maintenance, monitoring, and records are kept. b) Users have access to instructions for equipment and are aware of how to report an equipment problem. c) Staff are provided with suitable personal protective equipment.

Appendix 2: Classification of the level of shortfall

Where the HTA determines that a licensing standard is not met, the improvements required will be stated and the level of the shortfall will be classified as 'Critical', 'Major' or 'Minor'. Where the HTA is not presented with evidence that an establishment meets the requirements of an expected standard, it works on the premise that a lack of evidence indicates a shortfall.

The action an establishment will be required to make following the identification of a shortfall is based on the HTA's assessment of risk of harm and/or a breach of the HT Act or associated Directions.

1. **Critical shortfall:**

   A shortfall which poses a significant risk to human safety and/or dignity or is a breach of the Human Tissue Act 2004 (HT Act) or associated Directions

   or

   A combination of several major shortfalls, none of which is critical on its own, but which together could constitute a critical shortfall and should be explained and reported as such.

   A critical shortfall may result in one or more of the following:

   (1) A notice of proposal being issued to revoke the licence

   (2) Some or all of the licensable activity at the establishment ceasing with immediate effect until a corrective action plan is developed, agreed by the HTA and implemented.

   (3) A notice of suspension of licensable activities

   (4) Additional conditions being proposed

   (5) Directions being issued requiring specific action to be taken straightaway

2. **Major shortfall:**

   A non-critical shortfall that:

   - poses a risk to human safety and/or dignity, or
   - indicates a failure to carry out satisfactory procedures, or
   - indicates a breach of the relevant CoPs, the HT Act and other relevant professional and statutory guidelines, or
   - has the potential to become a critical shortfall unless addressed

   or

   A combination of several minor shortfalls, none of which is major on its own, but which, together, could constitute a major shortfall and should be explained and reported as such.

   In response to a major shortfall, an establishment is expected to implement corrective and preventative actions within 1-2 months of the issue of the final inspection report. Major shortfalls pose a higher level of risk and therefore a shorter deadline is given, compared to minor shortfalls, to ensure the level of risk is reduced in an appropriate timeframe.

3. **Minor shortfall:**

   A shortfall which cannot be classified as either critical or major, but which indicates a departure from expected standards.

This category of shortfall requires the development of a corrective action plan, the results of which will usually be assessed by the HTA either by desk based or site visit.

In response to a minor shortfall, an establishment is expected to implement corrective and preventative actions within 3-4 months of the issue of the final inspection report.

Follow up actions

A template corrective and preventative action plan will be sent as a separate Word document with both the draft and final inspection report. You must complete this template and return it to the HTA within 14 days of the issue of the final report.

Based on the level of the shortfall, the HTA will consider the most suitable type of follow-up of the completion of the corrective and preventative action plan. This may include a combination of

- a follow-up site-visit inspection
- a request for information that shows completion of actions
- monitoring of the action plan completion
- follow up at next desk-based or site-visit inspection.

After an assessment of your proposed action plan you will be notified of the follow-up approach the HTA will take.