Site visit inspection report on compliance with HTA licensing standards

Asterand UK Acquisition Limited

HTA licensing number 12353

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**

11 and 12 September 2017

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 Asterand UK Acquisition Limited had met the majority of the HTA's standards, two minor shortfalls were found. The minor shortfalls were in relation to sample traceability (standards T1(a) and T1(c)).

Particular examples of 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

Asterand UK Acquisition Ltd (the establishment) is a subsidiary of Asterand Bioscience, based in the United States of America (USA), which has recently become a subsidiary of the USA Bioreclamation-IVT group. The USA arm of Asterand distributes human tissue for research, but the UK subsidiary is only involved with this activity in exceptional circumstances. The establishment uses human tissue to develop and provide human tissue-based research solutions for Phase Zero pre-clinical studies on a commercial basis, to a client base primarily consisting of pharmaceutical companies.

The establishment is licensed by the HTA under the Human Tissue Act 2004 (HT Act) for the storage of relevant material which has come from a human body for the scheduled purpose of 'research in connection with disorders, or the functioning, of the human body' and provides commercial research services using this human tissue.

The establishment has been licensed by the HTA since June 2007 and was last inspected in November 2008. This report describes the second routine inspection of the establishment. In January 2015, a satellite site was added to the licence. Staff are not permanently based at the satellite but they do access the site to retrieve and return human tissue to the storage freezers housed there.

Samples stored at the establishment include cell pellets (e.g. fibroblasts and epithelial cells), snap frozen and Optimal Cutting Temperature compound (O.C.T) embedded tissue samples, and paraffin embedded blocks and tissue sections on microscope slides. Tissue samples stored include heart, lung, colon, testis, brain and other tissue types.

The majority of samples stored under the licence are obtained from the USA or from UK and European hospitals, and research tissue banks, under Service Level Agreements (SLAs) or Material Transfer Agreements requiring evidence of appropriate consent, or when applicable provided with the consent forms. Previously, finger-prick and venous blood samples have been obtained from an anonymised panel of establishment staff. This type of sample has not been collected in over two years, but may be required again in the future (see *Advice*, item 1). The establishment ensures that samples collected from the staff volunteer panel are appropriately consented, and documented informed consent is retained, on-site, by a member of staff with access to the original consent forms.

At the time of inspection, the establishment was storing a collection of paraffin embedded tissue blocks and tissue samples on microscope slides at room temperature, within a secure laboratory at the hub. The establishment was also storing 'snap' frozen tissue and O.C.T embedded tissue in -80°C freezers at the hub and satellite sites. All freezers were individually secured with key access, and were located either within an access-controlled laboratory (at the hub) or a secured storage facility (at the satellite site). Freezer temperatures at both the hub and satellite site were monitored, although the hub site was running their existing system in conjunction with the newer automated proprietary monitoring system in use at the satellite site, while they migrated their hub site monitoring to the new system. The -80°C freezers were monitored using the automated monitoring system, but temperatures were only

assessed for excursions from pre-defined ranges and not reviewed for temperature trends. Alarms were not routinely tested/challenged to ensure they were working as expected (e.g. within expected ranges and defined alarm criteria) (see *Advice*, item 11). Cell pellets were stored in liquid nitrogen (LN2) dewars, within a demarcated area in the access-controlled laboratory at the hub site. Two oxygen monitors, designed to be wearable, were arranged around the dewars, with the aim of monitoring for oxygen depletion in the event of LN2 leakage (see *Advice*, item 10).

All samples at the establishment, including relevant material stored under the HTA licence and non-relevant material such as cell lines, are logged into a bespoke software system on arrival at the establishment. This software is used to assign a unique identification code to the individual sample being received, but does not identify individual vials or individual pieces of tissue that are derived from the original sample (see shortfall against T1 (a)). The software is used to track sample receipt, storage, use and disposal. For management of LN2-stored sample inventory (primary cells and cell lines), staff in the laboratory also log samples into a separate spreadsheet, to routinely track changes to samples and their location on an interim basis, prior to the bespoke software being updated.

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 inspection included a visual inspection of both the hub and satellite, discussions and interviews with key staff, and a review of documentation. Interviews were held with the DI/CLHc, the PD, the Director of Scientific Operations and the Procurement Site Manager. There was also a roundtable discussion involving a number of staff working under the HTA licence.

Traceability audits were performed on 29 samples; comprising samples in -80°C storage, in LN2 storage, and paraffin embedded blocks and slides stored at room temperature. The samples were randomly selected from different locations within the storage facilities and labelling and location details were compared with the electronic and paper records. Samples were audited both from record to location, and from samples randomly identified in storage back to their electronic and paper records. Of the 29 samples included in the traceability audit, there were seven with minor discrepancies (e.g. lack of software-assigned ID, lack of aliquot number, sample not in expected location), and one sample could not be found (see shortfall against T1 (c)). However, after investigation all discrepancies could be accounted for, except for the missing sample which was not in the location identified in the tracking spreadsheet, after being moved due to LN2 storage issues (see shortfall against T1 (c)).This is being investigated by the establishment and will be followed up in the Corrective and Preventative Action plan resulting from this inspection.

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.

The DI is a Vice President at Asterand and the General Manager for UK Operations. As the senior member of staff in the UK, she has also been acting as the Corporate Licence Holder Contact (CLHc) for the purposes of the HTA licensing arrangements since 2012. However, the HTA's preferred model is for the DI and CLHc to be different people and, in discussion with the HTA, the DI will work with the Licence Holder to address this over the coming months. The recent changes in corporate structure provides a timely opportunity to review and update the governance structure with regard to the HTA licence. It is anticipated that the DI role will transfer to another suitable individual and the current DI will retain the role of the CLHc.

Compliance with HTA standards

While the majority of HTA standards were fully met by the establishment, two minor shortfalls were identified against two of the HTA's licensing standards.

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		
a) There is an identification system which assigns a unique code to each donation and to each of the products associated with it.	While each sample received into the establishment is assigned a unique identifier, used to identify it in the in-house tracking software, any individual pieces derived from the original sample retain the original ID. The tracking software notes the number of aliquots or tissue pieces comprising the sample (e.g. two x two bags indicating two pieces of 'snap' frozen tissue in two sample bags). To ensure sample traceability, individual sample vials and tissue pieces need to have a unique ID. For example, batches of vials containing the same sample could be labelled with an aliquot number, allowing the vial to be traced to a physical location in a storage box.	**Minor**

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.	Five samples in LN2 storage were audited. Racking in one of the storage dewars was previously damaged and removed, meaning that some samples had been moved to another dewar, with different sized storage boxes. The movement of samples was not updated in the in-house tracking software, but rather on an additional sample tracking spreadsheet in the lab. However, the tracking of the samples was found to be inaccurate as one sample could not be found in the box that it was recorded as having been moved to. Regular monthly audits indicate an average of 5-10% of 'in use' samples having tracking errors. See *Advice*, items 6 and 9.	**Minor**

Advice

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

No.	Standard	Advice
1.	GQ1(a)	The establishment has previously obtained fresh blood samples from a staff volunteer panel. The DI should review *SOP 589 Obtaining Fresh Blood Samples from the Asterand Volunteer Panel Version 8* to ensure that the processes described (e.g. the collection of venous blood and finger prick samples, collected at Asterand) are still relevant to the establishment's needs.
2.	GQ1(b)	The establishment maintains an electronic quality management system (eQMS) for their SOPs and other documentation. This includes a scanned copy of approved SOPs, with a handwritten date and signature on the front page. The hard copy of the document is kept in a folder. One SOP provided for the inspection had been annotated prior to the inspection, but not scanned into the eQMS. The DI is advised to review the auditing process to ensure the eQMS 'matches' the hard copy folder, and the process for 'releasing' approved SOPs to ensure that correct versions are released.
3.	GQ2(a)	The DI is advised to include audits of consent for individual samples into the existing audit schedule. This should provide assurances that appropriate consent is in place for the samples, and to ensure that individual consent forms are completed (when held on-site) or that suppliers are obtaining consent in accordance with the requirements of the HT Act and the HTA's Codes of Practice.
4.	GQ5(b)	The PD and DI have instituted a schedule of audits, including a monthly sample audit of 50 samples (record to location and vice versa) being used for current and/or recent projects. The audits are resolved individually, rather than taking into account the previous audit results, and routinely identify 5-10% errors in traceability. The DI is advised to undertake detailed analysis of these

		adverse events to identify any consistent issues or themes that can then be addressed to reduce the number of errors in the future and improve practices.
5.	GQ6(a)	Since their 2008 inspection and 2015 HTA Compliance Assessment, the establishment has documented a range of risk assessments. In April 2017, the HTA released an updated Code of Practice for Research. The DI should review the current risk assessments against the guidance in the updated Code to ensure that they cover the range of expected risk assessments and identify the risks inherent in the key activities. Where appropriate, procedures should be developed in consideration of and to mitigate these potential risks. Documented risk assessments should include an evaluation of the level of the risk and, where appropriate, the mitigating actions identified and the level of residual risk remaining. Risk assessments should include the risks relating to the premises, practices and procedures connected with licensed activities, including: • receiving and/or storing specimens without appropriate consent documentation; • storing or using human tissue after consent withdrawal; • storage failure or other damage affecting human tissue quality for useful research; • loss of human tissue; • sample mix-up or loss of traceability; • transport of specimens to and from the establishment; • security arrangements; • incorrect disposal.
6.	GQ6(a)	The DI is advised to risk assess the possibility of being unable to correctly identify a sample due to labelling issues. One sample vial audited from LN2 storage had been relabelled, but the new label was detaching from the vial. Two snap frozen tissue samples audited also had minor issues with labels. The text of one label was covered with ice and became smudged and difficult to read when the ice was rubbed away. Another snap frozen tissue sample was in a bag together with the label. The tissue had frozen over the label obscuring half of the label, the unique identifier was on the visible section of the label and traceability was maintained.
7.	T1(c)	Where there are multiple aliquots/vials in a sample batch, their location is logged to a specific box but not to a location within the box. The DI is advised to implement a tracking system that physically identifies the location that an individual vial is stored in (e.g. ‘position 11’ or ‘B1’).
8.	T1(c)	The establishment also stores samples that are not deemed Relevant Material under the HT Act. To avoid potential sample confusion, and to ensure that human tissue samples are handled in line with the regulatory requirements under the HT Act, the DI should assure herself that all freezers and containers holding human tissue are labelled appropriately.
9.	PFE2(a)	During the sample audit, there was a vial in LN2 storage that could not be located (see shortfall against T1 (c)). The vial had been stored in a large dewar where 2 racks had previously failed and been removed. There were no large dewars capable of re-housing the entire storage boxes from the racks in the large dewar and so individual vials were relocated to spaces in smaller boxes in the smaller dewars. This transfer was noted in the laboratory spreadsheet but not updated in the bespoke sample tracking software. During the audit, it appeared that the new sample location was transcribed into the laboratory spreadsheet incorrectly, resulting in the inability to locate the vial. In

		addition to addressing the traceability issues identified in this report, the DI is advised to review the current LN2 contingency arrangements in light of this occurrence, to determine if this error might occur in the future and could be mitigated e.g. by the provision of another dewar that would allow the transfer of an entire sample storage box.
10.	PFE2(c)	Two personal oxygen monitors, designed for wearable use, are wall-mounted at shoulder height around the LN2 dewars used for storing primary cells. Due to the manner in which LN2 leakages deplete oxygen following a spillage, the DI is advised to assess the risk of the oxygen monitors failing to detect oxygen depletion, as a result of LN2 spillage, due to their design, location and intended use.
11.	PFE2(c)	The DI is advised to regularly test and manually challenge the freezer alarms to ensure that they are operating as expected. Temperatures should be monitored using the continuous monitoring system to identify any trends that may herald impending equipment failure.

Concluding comments

This report outlines the second routine HTA site visit inspection of Asterand UK Acquisition Limited. Although three minor shortfalls were identified, a number of strengths and areas of good practice were observed during the inspection, including:

- The establishment observes a monthly ‘Good Practice Day’. This allows staff to ensure they are up to date on all their good practice commitments (e.g. to HTA compliance and a range of GxP practices). It also provides a set time when staff can be presented with further training or lessons learnt from ongoing audits, and other organisational advances. In addition to allowing all staff to maintain their competence and compliance, it represents a significant commitment of staff time and resource, for the establishment, that is spent on maintaining good practice throughout the organisation.

- The establishment has developed a validated ‘bespoke’ sample tracking software in house. The software was developed by, and is updated and maintained by the informatics manager at the establishment. This allows staff to actively participate in the development of the software, and to ensure it is developed in response to the needs and requirements of the staff using the software.

- Since the HTA inspection in 2008, the establishment has initiated a monthly sample tracking audit of 25 samples from sample to record, 25 samples from record to sample, and associated clinical records for all 50 samples.

There are a number of areas of practice that require improvement, including two 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: 06 October 2017

Report returned from DI: 26 October 2017

Final report issued: 07 November 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: 26 February 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.