Site visit inspection report on compliance with HTA licensing standards

Sygnature Discovery Ltd

HTA licensing number 12614

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**

22 June 2017

Summary of inspection findings

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

Although the HTA found that Sygnature Discovery Ltd had met the majority of the HTA's standards, five minor shortfalls were found with regard to the Consent (C), Governance and Quality Systems (GQS) and Facilities, Pemises and Equipment (PFE) standards. The shortfalls were in relation to documented consent procedures and training, documented procedures for the receipt, labelling and storage of relevant material, HTA related governance meetings and the monitoring of freezers. Advice has also been given relating to the C, GQS and PFE standards.

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 (DI) 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

This report refers to the activities carried out by Sygnature Discovery Ltd (the establishment). This was the second site inspection of the establishment visit since it was issued an HTA licence in February 2014. It was a routine site visit inspection to assess whether the establishment is meeting the HTA's licensing standards.

Sygnature Discovery Ltd is a commercial clinical research organisation founded in 2004 that provides contract research, focusing on pre-clinical drug discovery using *in vitro* cell models and biochemical based assays. All research is in response to client requests with no in-house directed research conducted. There are three groups within the organisation, two of which work under the HTA licence: Biosciences and Drug Metabolism and Pharmacokinetics (DMPK). The establishment has approximately 200 employees.

Sygnature Discovery Ltd is undergoing significant growth and has recently expanded into a new building in April 2017 to accommodate this. The current licence has been extended to cover the new site in Biocity 2 as well as the old site at Biocity.

Relevant material (from living and deceased donors) is stored for the scheduled purpose of: research in connection with disorders, or the functioning, of the human body ('research'). The establishment currently stores hepatocytes, peripheral blood mononuclear cells (PBMCs), whole blood and plasma. The establishment imports hepatocytes, PBMCs and plasma from commercial suppliers. Whole blood is also obtained from the Nottingham Health Science Biobank ('the Biobank'). A Blood Donor Panel has also been established to obtain whole blood from staff volunteers.

Consent

The DI has assurance that relevant material from outside establishments (e.g. commercial companies and the Biobank) has been sourced with appropriate consent and material transfer agreements are in place.

Healthy volunteer blood donors at the establishment are recruited via email. From expressions of interest, staff are invited to attend a meeting with the Blood Donor Manager to outline the research, discuss any risks involved and donors have the opportunity to ask questions. The donor information sheet is emailed in advance of this meeting. Written consent for donation of blood is taken and the volunteer is given 20 minutes to withdraw consent until the sample is processed. Consent is in place for one year; the donor will reconsent if continuing to donate blood after this period. Completed consent forms are stored in a secure location. All samples are link anonymised by the Blood Donor Panel Manager and rigorous procedures are in place to ensure donor confidentiality. The samples are procured at a nearby NHS walk-in centre approximately 500m from the establishment.

Receipt and labelling

Whole blood from the Biobank is collected by two members of staff from the establishment. This is logged onto the tissue inventory database using the original sample identifier and used within 48 hours of collection. Relevant material from commercial companies is received by the appropriate scientist and is logged onto the tissue inventory database using the original sample identifier. Whole blood received from healthy volunteers and client organisations are processed on the day of receipt. Both cellular and acellular fractions are used dependent on the experiment protocol and after experiment completion both acellular and cellular fractions are either decontaminated and disposed of or stored in a designated

-80°C freezer. The processing procedure is recorded in the electronic lab book of the individual responsible for the processing as well as on the electronic inventory log. Vials are not relabelled; the original identifier of the sample (e.g. supplier lot number) is recorded in the inventory. If multiple samples have the same identifier, no secondary numbering system is used to distinguish between individual vials (see Advice item 10). However, full traceability has been evidenced as the number of vials with the same lot number is recorded on the database inventory.

Storage

Storage of relevant material is either in one -80°C freezer or one liquid nitrogen (cryostorage) unit on level 4 within the DMPK group or in one -80°C freezer or one cryostorage unit on level 3 in the Bioscience group. Liquid nitrogen levels in the cryovessels are checked and filled twice per week and there is an audible alarm attached to these units. Samples are stored in the vapour phase and an audible alarm is triggered when liquid nitrogen levels fall below 25%. The monitoring system is not challenge tested.

Emergency back up -80°C freezers and space in alternative cryostorage units are available on site in the event of storage failure.

Disposal

Human tissue samples are used to exhaustion and disposed of according to health and safety and HTA guidelines. Human tissue that is unused is not disposed of unless poor quality or cellular viability issues are identified. The method, date and reason for disposal are recorded on the database inventory.

The inspection process

The timetable for the site inspection was developed after consideration of the establishment's previous inspection report, compliance update information and communications with the HTA since the last inspection.The inspection included a visual inspection of the site (sample reception and storage areas, research laboratories), discussions with the DI, two Senior Scientists within the Bioscience Group, a Senior Scientist within the DMPK group and the HR Advisor who is also the Blood Donor Manager. Audits of traceability were also carried out.

Traceability audits were performed on eight samples from commercial suppliers stored in liquid nitrogen and selected, at random, from the DMPK and Bioscience groups. These included two samples of PBMCs and two samples of T cells within the Bioscience Group and four samples of hepatocytes from the DMPK group. No samples from the biobank or from healthy volunteers were stored at the time of inspection. Full traceability was found.

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 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 Prractice.	There is no documented procedure for obtaining consent from staff for the donation of blood samples. *See Advice item 3*	**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 establishment could not provide evidence that staff seeking consent for storage and use of samples under the licence had received suitable training in seeking consent and the requirements of the HT Act. *See Advice item 4*	**Minor**

Governance and Quality

Standard	Inspection findings	Level of shortfall
GQ1 All aspects of the establishment's 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.	Although a storage policy is outlined within the *Human Tissue Authority Local Rules* document, there are no documented procedures for the collection, receipt, labelling and storage, of samples and the cleaning/decontamination of storage facilities.	**Minor**
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.	There are Health and Safety risk assessments relating to sample handling procedures but there are no risk assessments for licensed activities. *See Advice item 8*	**Minor**

Premises, Facilities and Equipment

Standard	Inspection findings	Level of shortfall
PFE2 There are appropriate facilities for the storage of bodies and human tissue		
c) Storage conditions are monitored, recorded and acted on when required.	The -80°C freezers of the DMPK and Bioscience groups are not being monitored for excursions out of acceptable temperature ranges and these acceptable temperature ranges are not documented. The monitoring systems of the liquid nitrogen cryovessels are not challenge tested.	**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 the current Persons Designated (PDs) on the licence to reflect staff who currently have most interaction with licensed activities. One of the current PDs is also the CLHc and this not appropriate for the role of PD as they are more senior than the DI. The DI is advised to consider appointing a staff member from the Blood Donor Panel as a PD on the licence to ensure consistent governance of this programme.
2.	C1d	The research undertaken could give rise to clinically significant results or incidental findings. Information regarding health related findings is included in the donor information sheet but donors should be given the opportunity to choose to receive this information or not and this should be part of the discussion with the donor during the consenting process. Information about health related findings in research can be found in the following document: https://wellcome.ac.uk/funding/managing-grant/wellcome-trust-policy-position-health-related-findings-research
3.	C1d	The DI is advised to consider that the consent procedure, consent forms, participant information sheets and consent training for the Blood Donor Panel are reviewed by a local research Committee.

4.	GQ3a	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 On completion of appropriate training, 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.
5.	GQ1b	The DI is advised to ensure all documents are controlled for version number, date of next review and that all documents have been reviewed by the stated date. Where documents are reviewed, the document version number should be updated so that it is clear that the document is a new version. Documents should include details of the author and reviewer, e.g. include version control for Donor Informed Consent Form and review date for Donor Information Sheet.
6.	GQ1d	Governance matters relating to HTA licensed activities are currently discussed at the Bioscience Management Group meetings. These meetings are currently not minuted therefore discussion of HTA related activities has not been evidenced. The DI is advised to instigate scheduled local HTA governance meetings with the new PDs, the CLHc and other staff where necessary and to ensure these meetings are minuted. HTA governance meetings can be used to discuss the identified shortfalls from this inspection and the need to address these shortfalls. The DI is also advised to consider including regular items such as the standardisation of documents, changes to standard operating procedures (SOPs), audits and their findings, competence and training, management of adverse events, risk assessments, equipment maintenance and updates from the HTA (e.g. e-newsletter items) in these meetings.
7.	GQ2a	The DI undertakes monthly storage location audits to routinely check and update the inventory of human tissue. The DI is advised to expand these audits to include traceability of the samples from consent documentation/ material transfer agreements to disposal. The DI is also advised to include an audit of consent forms for completion, legibility and accuracy. This will help to ensure that all consent forms are present and completed correctly and also help to identify whether any actions may be required where issues with consent forms are identified; for example, training requirements for those seeking consent.

		The DI is also advised to consider developing an audit schedule that includes horizontal audits to ensure that SOPs accurately reflect current practices. The results of all audit findings, and actions taken, should be formally recorded and discussed at the governance meetings, to ensure continuing improvement of processes and practices.
8.	GQ6a	The HTA Code E Research Standards and Guidance document gives further guidance on this (pages 12-13): 'All establishments should identify the risks inherent in the key activities, and procedures should be developed in consideration of and to mitigate these potential risks where appropriate. Establishments may tend to focus risk assessments on health and safety issues which, in themselves, are not sufficient to meet our standards. DIs should also assess the risks associated with licensed activities. 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. Risk assessments should be reviewed periodically (typically, every 1-3 years) and the actions to mitigate risks updated as necessary. Risk assessments should also be reviewed following an incident. By documenting risk assessments, staff are made aware of identified risks, which helps to prevent risks materialising and informs the development of procedures and relevant documentation.
9.	T1a	The inventory of samples within the Level 3 DMPK laboratory is a hand written record that is updated by staff as material is placed in or withdrawn from storage. This information is then transferred to the inventory database by the DI up to one week later. The DI is advised to implement a real-time record of storage on a backed up electronic database to mitigate the risk of loss of paper records and hence loss of traceability of samples.

10.	T1a	In consideration of sample labelling, the sample identifier is currently the original identifier from the supplier such as the lot number. Because of this, several vials do not have unique identifiers. The DI is advised to consider formalising the system for creating secondary, linked sample labels.
11.	PFE1c	At the time of inspection, relevant material was not being stored at -80°C but human tissue will be stored in the designated freezers in the future. There are no documented cleaning and decontamination schedules for these freezers at present. The DI is recommended to risk assess this and take actions in readiness for the future storage of relevant material.
12.	PFE2b	The establishment stores non-human material. To avoid mix-ups and ensure human tissue samples are handled in line with regulatory requirements under the HT Act, the DI is advised to ensure that non-human tissue is not stored alongside human tissue within the same cryobox in cryovessels.
13.	PFE2c	There are no oxygen monitoring alarms within the large laboratories housing the cryovessels which poses a risk to staff. The DI is recommended to risk assess the lack of oxygen level monitoring in these areas.
14.	PFE2c	To assist staff in following the correct procedure the DI is advised to consider placing labels on freezers and cryovessels to summarise the procedures to take when audible temperature alarms are activated.
15.	PFE3c	The DI is advised to ensure that all relevant cryovessels and freezers are labelled as storing samples under the licence and the details of who to contact in the event of any problems. This will help to raise awareness that samples are stored under the licence and ensure that any incidents or alarms are responded to appropriately.

Concluding comments

Although five minor shortfalls were identified, areas of strength and good practice were noted.

- In terms of strengths, staff are encouraged to develop and maintain their scientific knowledge and continued professional development, with a well-resourced training programme in place.
- In terms of good practice, there is a comprehensive donor information sheet and donor consent form which ensures multiple donations are not taken from volunteers and includes clear guidelines for those individuals who should not donate blood according to NHSBT criteria.

There are a number of areas of practice that require improvement, including 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: 19 July 2017

Report returned from DI: 28 July 2017

Final report issued: 8 August 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: 11 January 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.
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.

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.