Site visit inspection report on compliance with HTA minimum standards

ProImmune Ltd

HTA licensing number 12588

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**

2 July 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 ProImmune Ltd (the establishment) had met the majority of the HTA standards, two minor shortfalls were found with regard to the Governance and Quality Systems (GQS) standards. The shortfalls were in relation to governance meetings and risk assessments of practices. Advice has also been given relating to the Consent (C), GQS and Premises, Facilities and Equipment (PFE) standards, as well as to licence management.

Particular examples of good practice are included in the concluding comments section of the report.

The HTA's regulatory requirements

The HTA must assure itself that the Designated Individual (DI), Licence Holder (LH), premises and practices are suitable.

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

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

The HTA developed its licensing standards with input from its stakeholders. They are designed to ensure the safe and ethical use of human tissue and the dignified and respectful treatment of the deceased. The HTA inspects the establishments it 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 ProImmune Ltd (the establishment). This was the first site visit inspection of the establishment since it was issued an HTA licence in September 2011. It was a routine site visit inspection to assess whether the establishment is meeting the HTA's standards.

ProImmune Ltd is a private limited company, founded in 2000. It employs approximately 40 employees. The establishment is a Contract Research Organisation (CRO), providing a service to the research programmes of both sponsors and customers. 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 is exempt from the HTA's licensing arrangements. However, any samples which are retained following completion of the trial fall under the HTA licence.

Relevant material (from both living and deceased 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. The company's aim is to mimic and predict the function of the immune system by developing techniques which examine epitope-specific human immune cells using human leukocyte antigen (HLA) pentamers. The company also offers both antigen characterisation services and services for tracking antigen-specific immune responses.

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, and; samples from volunteers. Volunteer blood donations

include those from members of staff and those from specifically recruited external volunteer donors as part of a blood donation campaign.

Performance assessment work includes the preparation of calibration standards.

The establishment stores both normal and diseased human samples. These include isolated cellular preparations (buffy coats and leukocyte cones) and plasma samples.

Tissue is supplied to ProImmune Ltd from sources both within and outside the U.K. Agreements are in place with these organisations (*see Advice item 9*) for supply and transportation of the material.

The DI, the Person Designated (PD) and a specific project leader organise the volunteer blood donations. After reading information sheets regarding the donation, informed donor consent is sought by trained ProImmune staff and blood is taken by trained phlebotomists (*see Advice item 3*). Staff training in the seeking of consent is provided internally by trained staff members (*see Advice item 4*). The volunteer donations are de-identified and stored, pending use in research projects. Hard copies of the completed consent form are retained by the PD in secure storage.

Human tissue samples which are received into the establishment are logged onto paper 'sample handling forms' and into an electronic system, which is backed up. Tissue samples are allocated identity numbers referring to the particular study or project (*see Advice item 10*).

Upon receipt, samples are stored in the vapour phase in a liquid nitrogen tank. Those which require processing before long term storage are stored in a -80^{o}C freezer overnight, before being processed and transferred to liquid nitrogen storage.

Freezer and liquid nitrogen facilities are monitored and maximum and minimum temperatures are recorded on a daily basis. All tissue storage equipment is linked to a data-logged, continuous temperature monitoring facility which feeds into a wireless callout system. Temperature excursions outside the set ranges trigger both audible alarms and the wireless callout system. The liquid nitrogen storage area contains oxygen depletion monitors and there is an automatic cryofilling system for the tank. Power failure to the storage facilities and failure of the cryofilling system also trigger the audible alarms and the wireless callout system.

Emergency backup freezers and a contingent liquid nitrogen cryovessel are available in the event of storage failure.

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 (Company President and Chief Scientific Officer), the PD (Quality Specialist – Archival Services), the Assistant Services Manager and the Assay Team Leader. A documentation review and vertical and horizontal audits were carried out. Details of the two separate audits are provided below.

In the liquid nitrogen store, three samples were selected at random from the storage tank. The location details were compared to the paper and electronic records; no anomalies were found.

For the vertical audit, three samples were tracked from receipt to storage or use. One discrepancy was found in the audit for the transfer of samples from the -80^{o}C freezer to the liquid nitrogen tank. It was noted that there was a four day difference between date of receipt and date of transfer to liquid nitrogen storage and no storage location for this sample was recorded for this time period on either the paper or electronic records. Only a tick box present on the paper records indicated when samples had been transferred from the -80^{o}C freezer to the liquid nitrogen tank, with no operator signature or date of transfer being recorded (*see Advice item 8*).

Inspection findings

The HTA found the DI and the (Corporate) LH (CLH) to be suitable in accordance with the requirements of the legislation. There is currently no contact for the CLH (*see Advice item 1*).

Compliance with HTA standards

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 is no existing regular governance meeting which covers HTA issues for staff working under the licence. *See Advice item 5*.	**Minor**
GQ8 Risk assessments of the establishment's practices and processes are completed regularly and are recorded and monitored appropriately.	There are risk assessments related to Control of Substances Hazardous to Health (COSHH) risks of laboratory procedures. There are no risk assessments for activities relating to human tissue. *See Advice item 11*.	**Minor**

Advice

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

No.	Standard	Advice
1.	N/A	There is currently no CLH contact for the licence. The establishment is requested to appoint one and to notify the HTA as soon as possible.
2.	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
3.	C2	The donor information sheets 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. 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
4.	C3	The DI is advised to implement and document refresher training in consent for relevant staff to ensure that they are up to date in their knowledge.

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). 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.	Principally GQ2 but also relevant to standard GQ4	There is a detailed audit schedule which now needs to include audits related to human tissue. The DI is advised to create a human tissue audit schedule and divide it into small increments, carried out by different team members. The schedule could include process audits to ensure that SOPs accurately reflect current practices, vertical human tissue traceability audits, from records of receipt to storage, use or disposal, and horizontal audits. The DI may also wish to consider implementing a regular audit against HTA standards. The results of audit findings and actions taken should be formally recorded.
7.	GQ3	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/
8.	GQ4	The DI is advised to update the paper and electronic records to ensure that sample locations in both the liquid nitrogen tank and the -80^{o}C freezer are fully recorded in both formats.
9.	GQ5	Although the establishment endeavours to ensure that tissue suppliers obtain informed consent from donors by including such a statement in the terms and conditions section of its agreements, the DI may wish to consider modifications to this system. Examples seen in other establishments include issuing to each potential supplier a 'due diligence form', asking for details of ethical approval, ethical warranties, informed consent forms, consent warranties and regulatory compliance (where appropriate). A Material Transfer Agreement (MTA) is then constructed using these criteria as the supplier's responsibilities. By using such a method a list of 'approved suppliers' could be created for the establishment.
10.	GQ6	The DI may wish to consider using a system which allocates a unique identifier to each sample rather than a system which uses client project or study numbers.
11.	GQ8	Examples of such risk assessments could include – consent, sample receipt, labelling, sample loss and disposal of the wrong sample.
12.	PFE3	The DI is advised that freezers and cryovessels which contain human tissue are appropriately labelled to indicate this.

13.	PFE5	The DI is advised to ensure that both the freezers and the cryovessel containing human tissue are decontaminated and cleaned on a regular basis and that this is recorded.

Concluding comments

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

- The establishment has a small team which appears to work well together under the licence.
- There is a training schedule which comprehensively covers the regulatory requirements underlying consent, storage and use of human tissue.
- There is a detailed record of competence training, including training against SOPs.

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

The HTA requires that the Designated Individual 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: 4 August 2014

Report returned from DI: 19 August 2014

Final report issued: 15 September 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: 24 November 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)
GQ6 A coding and records system facilitates traceability of bodies, body parts, tissues and cells, ensuring a robust audit trail
• There is an identification system which assigns a unique code to each donation and to each of the products associated with it • An audit trail is maintained, which includes details of when and where the relevant material was acquired, the consent obtained, the uses to which the material was put, when the material was transferred and to whom

GQ7 There are systems to ensure that all adverse events are investigated promptly
• Corrective and preventive actions are taken where necessary and improvements in practice are made • System to receive and distribute national and local information (e.g. HTA communications)
GQ8 Risk assessments of the establishment's practices and processes are completed regularly and are recorded and monitored appropriately
• Documented risk assessments for all practices and processes • Risk assessments are reviewed when appropriate • Staff can access risk assessments and are made aware of local hazards at training

Premises, facilities and equipment standards
PFE1 The premises are fit for purpose
• A risk assessment has been carried out of the premises to ensure that they are appropriate for the purpose • Policies in place to review and maintain the safety of staff, authorised visitors and students • The premises have sufficient space for procedures to be carried out safely and efficiently • Policies are in place to ensure that the premises are secure and confidentiality is maintained
PFE 2 Environmental controls are in place to avoid potential contamination
• Documented cleaning and decontamination procedures • Staff are provided with appropriate protective equipment and facilities that minimise risks from contamination • Appropriate health and safety controls are in place
PFE3 There are appropriate facilities for the storage of bodies, body parts, tissues and cells, consumables and records.
• Relevant material, consumables and records are stored in suitable secure environments and precautions are taken to minimise risk of damage, theft or contamination • Contingency plans are in place in case of failure in storage area • Critical storage conditions are monitored and recorded • System to deal with emergencies on 24 hour basis • Records indicating where the material is stored in the premises

PFE 4 Systems are in place to protect the quality and integrity of bodies, body parts, tissues and cells during transport and delivery to a destination

- Documented policies and procedures for the appropriate transport of relevant material, including a risk assessment of transportation
- A system is in place to ensure that traceability of relevant material is maintained during transport
- Records of transportation and delivery
- Records are kept of any agreements with recipients of relevant material
- Records are kept of any agreements with courier or transport companies

PFE5 Equipment is appropriate for use, maintained, quality assured, validated and where appropriate monitored

- Records of calibration, validation and maintenance, including any agreements with maintenance companies
- Users have access to instructions for equipment and receive training in use and maintenance where appropriate
- Staff aware of how to report an equipment problem
- Contingency plan for equipment failure

Disposal Standards

D1 There is a clear and sensitive policy for disposing of human organs and tissue

- Documented disposal policy
- Policy is made available to the public
- Compliance with health and safety recommendations

D2 The reason for disposal and the methods used are carefully documented

- Standard operating procedures (SOPs) for tracking the disposal of relevant material detail the method and reason for disposal
- Where applicable, disposal arrangements reflect specified wishes

Appendix 2: Classification of the level of shortfall

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

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

1. **Critical shortfall:**

   A shortfall 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.