Site visit inspection report on compliance with HTA minimum standards

SCI Southampton

HTA licensing number 11053

Licensed for the

- **processing, storage and distribution of human tissues and cells for human application under the Human Tissue (Quality and Safety for Human Application) Regulations 2007**
- **storage of relevant Material which has come from a human body for use for a scheduled purpose**

4 November 2014

Summary of inspection findings

The HTA found the Designated Individual, the Licence Holder, the cryostorage area and the practices to be suitable in accordance with the requirements of the legislation. The HTA did not inspect the cleanroom as it was being refurbished following a failure of the ventilation system. This event was reported to the HTA and the actions taken and ongoing root cause analysis of the incident was discussed during the inspection.

SCI Southampton (the establishment) was found to have met all HTA standards in relation to the area where cells are received and processed using a closed sterile docking system, the cryostorage area and the practices. Currently all cells which require open processing are transferred to another HTA licensed SCI site. The HTA was assured that these changes have not had any impact on the supply of tissues to patients.

Particular examples of strengths and 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, Licence Holder, premises and practices are suitable.

The statutory duties of the Designated Individual are set down in Paragraph 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.

Licensable activities carried out by the establishment

'E' = Establishment is licensed to carry out this activity.

'E*' = Establishment is licensed to carry out this activity but is not currently carrying it out.

'TPA' = Third party agreement; the establishment is licensed for this activity but another establishment (unlicensed) carries out the activity on their behalf.

Tissue type	Procurement	Processing	Testing	Storage	Distribution	Import	Export
PBSC		**E**		**E**	**E**		
Bone Marrow		**E***		**E**	**E**		
DLI		**E***		**E**	**E**		

Background to the establishment and description of inspection activities undertaken

Stem Cells and Immunotherapies (SCI) is a specialist service within NHS Blood and Transplant (NHSBT). SCI Southampton (Steve Mills Stem Cell and Immunotherapies Department), the establishment, is one of several SCI laboratories in the UK and is located within the Southampton General Hospital site. The establishment is accredited for processing by the Joint Accreditation Committee – International Society for Cellular Therapy and the European Society for Blood and Marrow Transplantation. NHSBT is the corporate licence holder and the corporate licence holder contact is the Chief Executive Officer of NHSBT. The establishment has service level agreements (SLAs) with several other establishments which are licensed by the HTA for procurement, donor testing and distribution. These establishments seek donor consent, undertake donor evaluation, donor testing and send

stem cell harvests to SCI Southampton. The majority of stem cell harvests are for autologous use.

Stem cell harvests collected at other HTA licensed establishments are transported by dedicated couriers working under those licences and delivered to the establishment. In the case of harvests collected at Southampton General Hospital and Southampton Children's Hospital, establishment staff go to the apheresis collection centre to receive the stem cell harvest. Apheresis and bone marrow collections are placed together with plasma collections and transported in validated cool boxes containing ice packs. Upon receipt of the stem cells, a designated member of staff records the time, date, temperature of the shipment, details of packaging including the condition of the shipment, and the presence or absence of ice packs, on a standard form. These details are checked by a second member of staff and entered into a proprietary laboratory information management system.

Peripheral blood stem cells (PBSCs) are processed using a closed sterile docking system. The cryopreservative dimethylsuphoxide (DMSO) is diluted using plasma from the donor and cooled on packs of crushed ice. The diluted cryopreservative is added to the PBSCs, mixed and then divided between several cryogenic storage bags. The bags containing the cells are then transferred to one of three controlled rate freezers located in the cryopreservation and storage room. Samples of the mixture are also taken for sterility testing (anaerobic and aerobic bacteriology cultures) to detect contamination, and for archiving. Stem cells and donor lymphocytes are stored in the vapour phase of liquid nitrogen. Each liquid nitrogen storage vat is fitted with a local alarm. Two temperature probes, one within the liquid nitrogen and the other in the vapour phase of liquid are linked to the proprietary environmental monitoring system and are monitored remotely. This system also monitors the temperature of the products laboratory, quality testing laboratory, storage areas, fridges and environmental conditions within the clean room including the pressure differentials between rooms. Cryopreserved cells are transported in dry shippers which are cooled with liquid nitrogen in order to maintain the temperature below -150^{0}C. The temperature within the dry shipper is monitored using a temperature logger.

Cell potency assays (colony formation units) are undertaken on cells which have been cryopreserved for over five years. Swabs of the heat sealer and jaws of the sterile docking system are taken each week before and after cleaning in order to detect any contamination and to monitor the effectiveness of the cleaning method.

This was the fourth routine inspection of SCI Southampton and included a visual inspection of the premises, and interviews with the NHSBT Associate Director for Quality who is the DI, the Director of the Stem cell Laboratory, the Quality Assurance Manager, the Assistant Quality Assurance Manager and Specialist Biomedical Scientist. The establishment intends to process and store ovarian tissue in collaboration with an establishment which is licensed by the Human Fertilisation and Embryology Authority. Discussions were held with the Advanced Specialist for Ovarian Tissue and the Lead Quality Specialist with NHSBT which covered the validation of the process and submission of a preparation process dossier (PPD) to the HTA for authorisation.

Actions taken following the recent cleanroom failure were also discussed. The HTA understands that there was a sudden failure of the airflow system in the clean room. No downward trend in air pressure was noted by the building management system and so there was no warning that such a failure was likely to take place. The cleanroom had been maintained every six months by an external contractor when checks were undertaken on the filter integrity, filter flow rates, air changes and particle counts. The HTA will continue to monitor the actions being taken by the establishment including installation of audible alarms, refurbishment and revalidation of the cleanroom.

A document review was undertaken; documents reviewed included the Quality Management Plan, standard operating procedures (SOPs) relating to the processing of stem cells, environmental monitoring using contact plates, settle plates and swabs, audit reports, cleaning records, service level agreements, meeting minutes, incident (deviations) reports including corrective actions taken, staff training and validation records and engraftment reports. Traceability from donor files to storage locations as noted in computer records were also checked. Competency records of cleanroom personnel including the gowning procedure and aseptic techniques were also reviewed.

Audit trails were undertaken of four stem cells received by the establishment -

a) Receipt, quality assessment, packaging and issue of fresh stem cells received from a HTA licensed registry for allogeneic use, and the cryopreservation and storage of five bags containing donor lymphocyte infusions. In this case staff transferred the fresh stem cells in a validated cool box containing ice packs, to Southampton General Hospital.

b) Receipt, cryopreservation and storage of stem cells harvested at another HTA licensed site from an adult for autologous use.

c) Receipt, cryopreservation, storage, packaging and release of stem cells harvested at another HTA licensed site from an adult for autologous use. The records included details of packaging in the dry shipper when transported to the enduser, and records stored by the dry shipper temperature log.

d) Receipt, cryopreservation, storage and disposal records relating to a bone marrow harvest from a paediatric donor which also included records of the colony formation unit test results.

In each case, donor files containing forms and records relating to receipt and processing of stem cells were reviewed. They included records of receipt (date, time, temperature of transported cells), details of apheresis, haematology analyser results (total nucleotide cell count, lymphocyte counts, monocyte and platelet counts), flow cytometry results (cell markers such as CD3, CD34, CD45 and viability estimates using 7-aminoactinomycinD), freezing profile as recorded by the controlled rate freezer and pre-processing and post-processing cleaning records.

There were no discrepancies.

Inspection findings

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

Compliance with HTA standards

All applicable HTA standards have been assessed as fully met.

Advice

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

No.	Standard	Advice
1.	GQ1	The DI is advised to implement a system of checks to ensure that the quality of work undertaken in the cleanroom by external contractors, meets with the

		requirements of the contract.
2.	GQ4	The DI is advised to consider using files with fasteners to ensure that all records in a donor file are filed securely. The folders currently in use contain paper records which are loosely filed and there is the risk that these records can be easily misplaced, particularly when several files are reviewed at the same time. The HTA notes that many of these records are also present in electronic form and can be accessed if required.
3.	GQ8	The DI is advised to risk assess the systems in place to monitor the supply of air to the clean room in order to ensure that staff are provided with some warning of the likelihood of a potential failure in the air supply.
4.	PFE2	The DI is advised to consider installing an audible alarm system and undertake regular tests of the audible alarm system, once it has been installed in the cleanroom. The tests must include checks on the response by building maintenance personnel and switchboard. The DI is advised to consider implementing a system of manual checks of air pressure readings in the clean room for a fixed period of time following the re-validation of the cleanroom. Manual recording of the air pressure would provide additional assurance of the accuracy of the building management system.

Concluding comments

Several areas of good practice were identified during the inspection. The establishment has committed staff who work well together as a team. Regular meetings take place with staff based at other HTA licensed establishments who send stem cell harvests to SCI Southampton for processing and storage. The establishment follows up engraftment data for all products, which helps to provide assurance that processing undertaken at the SCI laboratory continues to achieve the intended results.

Comprehensive quality checks are undertaken on products before and after cryopreservation. Key processing records and labels used on the final products are checked and signed by a second member of staff. The Quality Assurance Department at NHSBT has overall responsibility for quality and supports staff at the establishment to control and monitor non-conformances. Dedicated quality assurance personnel at SCI Laboratory meet regularly with laboratory staff to review incidents and corrective and preventative actions taken following these incidents, thus demonstrating their commitment to continuous improvement.

The HTA has given advice to the Designated Individual with respect to installing and testing audible alarms, undertaking risk assessments in relation to monitoring of the cleanroom, filing of documents and manual recording of the air pressure across rooms in the clean room.

The HTA has assessed the establishment as suitable to be licensed for the activities specified.

Report sent to DI for factual accuracy: 1 December 2014

Report returned from DI: 10 December 2014

Final report issued: 19 December 2014

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.

Human Tissue (Quality and Safety for Human Application) Regulations 2007 Standards

Governance and Quality

Standard
GQ1 All aspects of the establishment's work are supported by ratified documented policies and procedures as part of the overall governance process.
a) There is an organisational chart clearly defining the lines of accountability and reporting relationships.
b) There are procedures for all licensable activities that ensure integrity of tissue and / or cells and minimise the risk of contamination.
c) There are regular governance meetings, for example health and safety, risk management and clinical governance committees, which are recorded by agendas and minutes.
d) There is a document control system to ensure that changes to documents are reviewed, approved, dated and documented by an authorised person and only current documents are in use.
g) There are procedures to ensure that an authorised person verifies that tissues and / or cells received by the establishment meet required specifications.
h) There are procedures for the management and quarantine of non-conforming consignments or those with incomplete test results, to ensure no risk of cross contamination.
i) There are procedures to ensure tissues and / or cells are not released from quarantine until verification has been completed and recorded.
j) There are procedures detailing the critical materials and reagents used and where applicable, materials and reagents meet the standards laid down by the European directives on medical devices and in vitro diagnostic medical devices.
k) There is a procedure for handling returned products.
l) There are procedures to ensure that in the event of termination of activities for whatever reason, stored tissues and / or cells are transferred to another licensed establishment or establishments.
m) The criteria for allocating tissues and / or cells to patients and health care institutions are documented and made available to these parties on request.
o) There is a complaints system in place.
p) There are written agreements with third parties whenever an activity takes place that has the potential to influence the quality and safety of human tissues and / or cells.
q) There is a record of agreements established with third parties.
r) Third party agreements specify the responsibilities of the third party and meet the requirements set out in Directions 003/2010.

s) Third party agreements specify that the third party will inform the establishment in the event of a serious adverse reaction or event.
t) There are procedures for the re-provision of service in an emergency.
GQ2 There is a documented system of quality management and audit.
a) There is a quality management system which ensures continuous and systematic improvement.
b) There is an internal audit system for all licensable activities.
c) An audit is conducted in an independent manner at least every two years to verify compliance with protocols and HTA standards, and any findings and corrective actions are documented.
d) Processes affecting the quality and safety of tissues and / or cells are validated and undergo regular evaluation to ensure they continue to achieve the intended results.
GQ3 Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills.
a) There are clearly documented job descriptions for all staff.
b) There are orientation and induction programmes for new staff.
c) There are continuous professional development (CPD) plans for staff and attendance at training is recorded.
d) There is annual documented mandatory training (e.g. health and safety and fire).
e) Personnel are trained in all tasks relevant to their work and their competence is recorded.
f) There is a documented training programme that ensures that staff have adequate knowledge of the scientific and ethical principles relevant to their work, and the regulatory context.
g) There is a documented training programme that ensures that staff understand the organisational structure and the quality systems used within the establishment.
h) There is a system of staff appraisal.
i) Where appropriate, staff are registered with a professional or statutory body.
j) There are training and reference manuals available.
k) The establishment is sufficiently staffed to carry out its activities.
GQ4 There is a systematic and planned approach to the management of records.
a) There are procedures for the creation, identification, maintenance, access, amendment, retention and destruction of records.
b) There is a system for the regular audit of records and their content to check for completeness, legibility and accuracy and to resolve any discrepancies found.
c) Written records are legible and indelible. Records kept in other formats such as computerised records are stored on a validated system.
d) There is a system for back-up / recovery in the event of loss of computerised records.

e) The establishment keeps a register of the types and quantities of tissues and / or cells that are procured, tested, preserved, processed, stored and distributed or otherwise disposed of, and on the origin and destination of tissues and cells intended for human application.
f) There are procedures to ensure that donor documentation, as specified by Directions 003/2010, is collected and maintained.
g) There is a system to ensure records are secure and that donor confidentiality is maintained in accordance with Directions 003/2010.
h) Raw data which are critical to the safety and quality of tissues and cells are kept for 10 years after the use, expiry date or disposal of tissues and / or cells.
i) The minimum data to ensure traceability from donor to recipient as required by Directions 003/2010 are kept for 30 years after the use, expiry or disposal of tissues and / or cells.
j) Records are kept of products and material coming into contact with the tissues and / or cells.
k) There are documented agreements with end users to ensure they record and store the data required by Directions 003/2010.
l) The establishment records the acceptance or rejection of tissue and / or cells that it receives and in the case of rejection why this rejection occurred.
m) In the event of termination of activities of the establishment a contingency plan to ensure records of traceability are maintained for 10 or 30 years as required.
GQ5 There are documented procedures for donor selection and exclusion, including donor criteria.
a) Donors are selected either by the establishment or the third party acting on its behalf in accordance with the criteria required by Directions 003/2010.
b) The testing of donors by the establishment or a third party on behalf of the establishment is carried out in accordance with the requirements of Directions 003/2010.
d) There is a system in place either at the establishment or at a third party acting on its behalf to record results of donor selection and associated tests.
e) Testing of donor samples is carried out using CE marked diagnostic tests.
GQ6 A coding and records system facilitates traceability of tissues and / or cells, ensuring a robust audit trail.
a) There is a donor identification system which assigns a unique code to each donation and to each of the products associated with it.
b) An audit trail is maintained, which includes details of when the tissues and / or cells were acquired and from where, the uses to which the tissues and / or cells were put, when the tissues and / or cells were transferred elsewhere and to whom.
c) The establishment has procedures to ensure that tissues and / or cells imported, procured, processed, stored, distributed and exported are traceable from donor to recipient and vice versa.
GQ7 There are systems to ensure that all adverse events, reactions and/or incidents are investigated promptly.
a) There are procedures for the identification, reporting, investigation and recording of adverse

events and reactions, including documentation of any corrective or preventative actions.
b) There is a system to receive and distribute national and local information (e.g. HTA regulatory alerts) and notify the HTA and other establishments as necessary of serious adverse events or reactions.
c) The responsibilities of personnel investigating adverse events and reactions are clearly defined.
d) There are procedures to identify and decide the fate of tissues and / or cells affected by an adverse event, reaction or deviation from the required quality and safety standards.
e) In the event of a recall, there are personnel authorised within the establishment to assess the need for a recall and if appropriate initiate and coordinate a recall.
f) There is an effective, documented recall procedure which includes a description of responsibilities and actions to be taken in the event of a recall including notification of the HTA and pre-defined times in which actions must be taken.
g) Establishments distributing tissue and / or cells provide information to end users on how to report a serious adverse event or reaction and have agreements with them specifying that they will report these events or reactions.
h) Establishments distributing tissues and / or cells have systems to receive notifications of serious adverse events and reactions from end users and notify the HTA.
GQ8 Risk assessments of the establishment's practices and processes are completed regularly and are recorded and monitored appropriately.
a) There are documented risk assessments for all practices and processes.
b) Risk assessments are reviewed regularly, as a minimum annually or when any changes are made that may affect the quality and safety of tissues and cells.
c) Staff can access risk assessments and are made aware of local hazards at training.
d) A documented risk assessment is carried out to decide the fate of any tissue and / or cells stored prior to the introduction of a new donor selection criteria or a new processing step, which enhances the quality and safety of tissue and / or cells.

Premises, Facilities and Equipment

Standard
PFE1 The premises are fit for purpose.
a) A risk assessment has been carried out of the premises to ensure that they are fit for purpose.
b) There are procedures to review and maintain the safety of staff, visitors and patients.
c) The premises have sufficient space for procedures to be carried out safely and efficiently.
e) There are procedures to ensure that the premises are secure and confidentiality is maintained.
f) There is access to a nominated, registered medical practitioner and / or a scientific advisor to provide advice and oversee the establishment's medical and scientific activities.

PFE2 Environmental controls are in place to avoid potential contamination.
a) Tissues and / or cells stored in quarantine are stored separately from tissue and / or cells that have been released from quarantine.
b) Where processing of tissues and / or cells involves exposure to the environment, it occurs in an appropriate, monitored environment as required by Directions 003/2010.
c) There are procedures for cleaning and decontamination.
d) Staff are provided with appropriate protective clothing and equipment that minimise the risk of contamination of tissue and / or cells and the risk of infection to themselves.
PFE3 There are appropriate facilities for the storage of tissues and / or cells, consumables and records.
a) Tissues, cells, consumables and records are stored in secure environments and precautions are taken to minimise risk of damage, theft or contamination.
b) There are systems to deal with emergencies on a 24 hour basis.
c) Tissues and / or cells are stored in controlled, monitored and recorded conditions that maintain tissue and / or cell integrity.
d) There is a documented, specified maximum storage period for tissues and / or cells.
PFE4 Systems are in place to protect the quality and integrity of tissues and / or cells during transport and delivery to its destination.
a) There is a system to ensure tissue and / or cells are not distributed until they meet the standards laid down by Directions 003/2010.
b) There are procedures for the transport of tissues and / or cells which reflect identified risks associated with transport.
c) There is a system to ensure that traceability of tissues and / or cells is maintained during transport.
d) Records are kept of transportation and delivery.
e) Tissues and / or cells are packaged and transported in a manner and under conditions that minimise the risk of contamination and ensure their safety and quality.
f) There are third party agreements with courier or transport companies to ensure that any specific transport conditions required are maintained.
g) Critical transport conditions required to maintain the properties of tissue and / or cells are defined and documented.
h) Packaging and containers used for transportation are validated to ensure they are fit for purpose.
i) Primary packaging containing tissues and / or cells is labelled with the information required by Directions.
j) Shipping packaging containing tissues and / or cells is labelled with the information required by Directions.

PFE5 Equipment is appropriate for use, maintained, quality assured, validated and where appropriate monitored.
a) Critical equipment and technical devices are identified, validated, regularly inspected and records are maintained.
b) Critical equipment is maintained and serviced in accordance with the manufacturer's instructions.
c) Equipment affecting critical processes and storage parameters is identified and monitored to detect malfunctions and defects and procedures are in place to take any corrective actions.
d) New and repaired equipment is validated before use and this is documented.
e) There are documented agreements with maintenance companies.
f) Cleaning, disinfection and sanitation of critical equipment is performed regularly and this is recorded.
g) Instruments and devices used for procurement are sterile, validated and regularly maintained.
h) Users have access to instructions for equipment and receive training in the use of equipment and maintenance where appropriate.
i) Staff are aware of how to report an equipment problem.
j) For each critical process, the materials, equipment and personnel are identified and documented.
k) There are contingency plans for equipment failure.

Disposal

Standard
D1 There is a clear and sensitive policy for disposing of tissues and / or cells.
a) The disposal policy complies with HTA's Codes of Practice.
b) The disposal procedure complies with Health and Safety recommendations.
c) There is a documented procedure on disposal which ensures that there is no cross contamination.
D2 The reasons for disposal and the methods used are carefully documented.
a) There is a procedure for tracking the disposal of tissue and / or cells that details the method and reason for disposal.
b) Disposal arrangements reflect (where applicable) the consent given for disposal.

Appendix 2: Classification of the level of shortfall (HA)

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 direct risk of causing harm to a recipient patient or to a living donor,

   Or

   A number of 'major' shortfalls, none of which is critical on its own, but viewed cumulatively represent a systemic failure and therefore are considered 'critical'.

   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.

   A shortfall in the carrying out of licensable activities which poses an indirect risk to the safety of a donor or a recipient

   or

   A shortfall in the establishment's quality and safety procedures which poses an indirect risk to the safety of a donor or a recipient;

   or

   A shortfall which indicates a major deviation from the **Human Tissue (Quality and Safety for Human Application) Regulations 2007** or the **HTA Directions**;

   or

   A shortfall which indicates a failure to carry out satisfactory procedures for the release of tissues and cells or a failure on the part of the designated individual to fulfil his or her legal duties;

   or

   A combination of several 'minor' shortfalls, none of which is major on its own, but which, viewed cumulatively, could constitute a major shortfall by adversely affecting the quality and safety of the tissues and cells.

   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 and, which can be addressed by further development by the establishment.

   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 review or at the time of the next inspection.

   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.