Site visit inspection report on compliance with HTA minimum standards

Smart Cells International Limited
HTA licensing number 22522
Licensed for the

- **procurement, processing, testing, storage, distribution and import/export of human tissues and cells for human application under the Human Tissue (Quality and Safety for Human Application) Regulations 2007**

8 May 2013

Summary of inspection findings

The HTA found that Smart Cells International Limited (the establishment) had met the majority of HTA standards, however a number of shortfalls were found in relation to the standards of (i) Consent, (ii) Governance and Quality; and (iii) Premises, Facilities and Equipment.

The establishment has worked to address shortfalls identified at the last inspection, but further work is needed to address the risk of microbiological contamination from umbilical cord tissue, identified during the last inspection.

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, Licence Holder, premises and practices are suitable.

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.

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
UCB	**TPA**	**E**	**TPA**	**E**	**E***	**E**	**E***
UCT	**TPA**	**E**	**TPA**	**E**	**E***	**E**	**E***

(UCB – Umbilical Cord Blood; UCT – Umbilical Cord Tissue)

Background to the establishment and description of inspection activities undertaken

Smart Cells International is licensed under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (the Quality and Safety Regulations) for the procurement, testing, processing, storage, distribution and import and export of umbilical cord blood stem cells (UCB) and umbilical cord tissue (UCT). Currently, processed material is intended for either autologous use or, potentially, directed donation to relatives.

UCB and UCT are procured (under TPA) within the UK and by international partner offices both within and outside the European Economic Area **(**EEA). All samples are transported by courier to the establishment, where processing and storage of samples is undertaken. UCB and UCT are receipted into the establishment by trained personnel and then passed through into the processing facility where they are processed in separate rooms. UCB is processed using a closed system designed to not permit environmental exposure. UCT undergoes processing for cryopreservation in a Grade A cabinet. Since the last inspection, the way in which the Grade A area is monitored has been amended: continuous particle monitoring is carried out during critical processing steps and environmental monitoring is carried out for every processing session. Following cryopreservation, UCB and UCT are transferred into separate liquid nitrogen vessels for long term storage at the establishment.

Mandatory serology testing and microbiology testing are carried out by third party laboratories within the UK under the terms of a TPA. One EEA and one non-EEA partner undertake serology testing at source.

The establishment has previously been inspected in June 2009 and May 2011. This site visit was a third routine inspection which also provided an opportunity for the HTA to review the establishment following a change in Designated Individual (DI) in March 2012. The new DI is the Quality Manager for the facility.

As part of the inspection process, interviews were conducted with key members of staff working under the licence. In addition to the DI, these included the Operations Manager and individuals involved in obtaining consent and tissue processing. A new member of staff was interviewed to discuss induction and staff training programmes.

A visual inspection of the premises was performed and covered the sample receipt and consumables storage areas, processing laboratories and cryostorage tanks.

A review of quality documentation was carried out, including the quality manual, staff training records, policy and procedural documents, processing records and risk assessments.

During the inspection, audits were conducted to assess traceability of stored samples. Two UCB and two UCT samples, that had been processed and stored, were traced from records to their location in the storage tank, or from the location in the storage tank to associated records. No anomalies were found for three of the samples, the fourth sample was correctly located in the storage tank, however the processing records were unavailable for review as they had been sent to be scanned for archive.

Inspection findings

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

HTA standards not met:

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.		
d) Consent forms comply with the HTA's Codes of Practice.	Responsibilities of both the establishment and the third party relating to procurement should be accurately reflected in all agreements and client information, to ensure that consent is obtained in an informed manner. The client storage agreement states that 'SCI is not responsible for any failures in the collection of any Sample.' Further to this, the client consent form states that 'SCI is not responsible for the collection of the cord blood/cord tissue and its storage prior to collection by the appointed courier service'. The DI understands that the establishment has responsibility for all licensable activities, including those carried out by third parties under the terms of a TPA. Responsibilities of each party are outlined, where relevant, within TPAs, but are not reflected in client documentation relating to consent. *Since the inspection, the establishment has provided the HTA with information that has been assessed as sufficient to demonstrate that this shortfall has been addressed (04 October 2013).*	**Minor**

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.		
	A number of the establishment's policies do not reflect current practices. Examples of this are evidenced as shortfalls against GQ1b, GQ5b, PFE3b and PFE4b. This is not an exhaustive list of examples and advice in relation to this shortfall has been issued to the DI regarding audit (see Advice item 5). The inconsistencies between policy and practice are collectively considered to be a major shortfall against licensing standard GQ1. Further specific items contributing towards a shortfall against this standard are outlined below.	**Major**
b) There are procedures for all licensable activities that ensure integrity of tissue and / or cells and minimise the risk of contamination.	Refer to the shortfall against PFE3a.	
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.	All documentation currently in use should be within an appropriate review date however, the document control system does not robustly ensure that only current versions of documents are in use. Some key documents seen by the inspection team were beyond the recorded review date (e.g. Validation Policy S PD 007, due for review in April 2012). The version of BS004 SOP currently in use is Revision 7, however the final page of this SOP was from an earlier revision of the document (Revision 6). In addition, the Quality Manual states that it is reviewed annually, but is marked for review every two years.	
r) Third party agreements specify the responsibilities of the third party and meet the requirements set out in Directions 003/2010.	Refer to the shortfall relating to GQ5b. *Since the inspection, the establishment has provided the HTA with information that has been assessed as sufficient to demonstrate that this shortfall has been addressed (06 September 2013).*	

GQ2 There is a documented system of quality management and audit.		
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.	There is an audit system set up to review licensable activities, however these audits are carried out by the DI who is not sufficiently independent from licensable activities. The current system cannot ensure that audits maintain impartiality. *Since the inspection, the HTA has been advised by establishment that a suitable individual has been identified and that an independent audit will be incorporated into the audit schedule. This action was completed prior to the issue of the final report.*	**Minor**
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.	On the day of inspection, the establishment were unable to demonstrate that regular evaluation and validation of critical processes was being carried out across the organisation. Staff were asked about validation of parameters relating to sample shipping, processing and cryopreservation and were unable to demonstrate that critical quality attributes relevant to the quality and safety of tissues and cells had been subject to validation and regular evaluation. Specific points relating to UCB and UCT processing are outlined in the bulleted points below (Refer also to Advice item 8). • Processing of UCB is carried out according to historical validation. This needs to be updated to consider current practices, including the number of samples processed by the establishment at any time. For example, when samples from multiple clients are processed simultaneously, the timing between addition of cryopreservative and commencement of controlled rate freezing should be evaluated and validated. • Processing of UCT is undertaken by the establishment, with the intention of storing stem cells contained within this tissue (see Advice item 2). However, the	**Major**

	establishment has not demonstrated, through validation, that their processing method is able to achieve this In the Client Storage Agreement, the establishment states that it will store samples provided that 'the cord tissue is in an acceptable state', but does not define validated limits of what this acceptable state is. After the last inspection, the establishment carried out a study to characterise the extent of microbiological contamination present in UCT samples. Further validation is needed to ensure that the results of the last study are appropriately acted up, in order to determine (i) whether it is possible to reduce, through additional processing, the extent of contamination in UCT samples and (ii) that viable cells can be recovered from contaminated tissue. Refer also to the related shortfalls regarding storage UCT (GQ1b and PFE3a). As noted above, the copy of the establishment's validation policy had also exceeded the stated review date. For both UCB and UCT, the maximum allowable time, between procurement of samples and processing, also requires validation. Further to this, when samples are received into the establishment, there are circumstances under which they may not be processed immediately and could be kept at room temperature. This practice and any validated circumstances under which it is acceptable are not currently mentioned in processing SOPs e.g. BS004. A major shortfall relating to the validation of transport parameters was also found relating to standard PFE4.	

GQ5 There are documented procedures for donor selection and exclusion, including donor criteria.		
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.	A number of quality documents relating to donor testing do not reference HTLV-1 testing. These include the TPA in place with the UK testing facility, the risk assessment for processing umbilical cord blood and cord tissue (RA LAB 002) and the SOP for actions to be taken for client blood samples with a positive result following mandatory testing (AS 032). This SOP should also be updated to reference current HTA Directions. This also falls as a shortfall against standard GQ1r. *Since the inspection, this documentation has been reviewed and updated. This action was completed prior to the issue of the final report.*	**Minor**
GQ7 There are systems to ensure that all adverse events 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.	The protocol for Serious Adverse Event Reporting (GM 003) captures Serious Adverse Events but should also include Serious Adverse Reactions. This protocol also refers to the reporting requirement to the HTA as within 24 hours of the SAE being reported to the establishment, rather than within 24 hours of discovery. *Since the inspection, this documentation has been reviewed and updated. This action was completed prior to the issue of the final report.*	**Minor**
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.	Refer to the shortfall against licensing standard PFE4a.	

Premises, Facilities and Equipment

Standard	Inspection findings	Level of shortfall
PFE2 Environmental controls are in place to avoid potential contamination.		
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.	The establishment has demonstrated that microbiological contamination is not eliminated from samples during processing (see shortfalls against GQ1b and PFE3a), and because of this are not using environmental monitoring data to reassure themselves that contaminants are not being introduced during processing of UCT. Volume 4, Annex 1 of the Eudralex Good Manufacturing Practice (GMP) guidelines states that 'results from monitoring should be considered when reviewing batch documentation for finished product release' (paragraph 18) and that 'appropriate alert and actions should be set out for the results of particulate and microbiological monitoring. If these limits are exceeded operating procedures should prescribe corrective action.' (Paragraph 20) The current system for reviewing environmental monitoring data does not consider what corrective actions should be put in place when an environmental monitoring alert limit is reached, and how these actions should be documented. When processing deviates from a Grade A environment, there is no procedure in place that would allow this to be considered as part of a concessionary release procedure (refer to the shortfalls against GQ7d and PFE4a). For example, deviations from protocol are not reflected in batch records with respect to microbial contamination, such as finger dabs and settle plate data. This monitoring data is required in order to demonstrate that processing is occurring in a Grade A environment. Refer also to Advice item 9. *Since the inspection, the establishment has provided the HTA with information that has been assessed as sufficient to demonstrate that this shortfall has been addressed (15 August 2013).*	**Major**

PFE3 There are appropriate facilities for the storage of bodies, body parts, tissues, 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.	Storage boxes contain vials of UCT from more than one client. Microbiological testing of UCT samples by the establishment has demonstrated that processing does not remove contamination from these samples. There is a risk of microbiological cross-contamination posed by storing vials in this manner. The establishment should provide evidence of validation, which demonstrates that the manner in which contaminated samples are stored does not pose a risk of cross-contamination by microbiological contaminants. Refer also to GQ1b and GQ2d. *Since the inspection, the establishment has provided the HTA with information that has been assessed as sufficient to demonstrate that this shortfall has been addressed (04 November 2013*).	**Minor**
b) There are systems to deal with emergencies on a 24 hour basis.	The vial storage freezer for UCT is not currently linked to an alarm system and so staff would not be made aware of any significant temperature deviations and consequent alarm alerts out of hours. The establishment should document the risks associated with maintaining the vial storage freezer in this manner and ensure that this practice is accurately reflected within relevant policies, protocols and client information. *Since the inspection, the establishment has provided the HTA with information that has been assessed as sufficient to demonstrate that this shortfall has been addressed (06 September 2013).*	**Minor**

PFE4 Systems are in place to protect the quality and integrity of bodies, body parts, tissues and cells during transport and delivery to a 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.	The procedure for release of samples processed for transplantation (BS 018) does not include a concessional release procedure for non-conforming products. Refer also GQ7d and the associated shortfalls against GQ1b, PFE2b and PFE3a. *Since the inspection, the establishment has provided the HTA with information that has been assessed as sufficient to demonstrate that this shortfall has been addressed (15 August 2013).*	**Minor**
b) There are procedures for the transport of tissues and / or cells which reflect identified risks associated with transport. 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.	One of the establishment's policies states that the collection kit is designed and validated to maintain samples between 14-28°C and that samples known to have been exposed to temperatures outside of this range will be processed as a variance. In practice this is not achievable as the establishment does not monitor temperature during each shipment. Although the temperature inside shipping containers is periodically monitored using data loggers, the policy does not reflect current practice as temperature during shipping is not assessed for each procurement. The HTA also requires evidence of current validation of shipping parameters, including time elapsed between procurement and processing and temperature of samples in this time period, to ensure that the quality and safety of tissues and cells is maintained during transit.	**Major**

Advice

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

No.	Standard	Advice
1.	-	The DI is advised to appoint a Person Designated who is able to oversee licensable activity in the absence of the DI.
2.	C1d	The DI is advised to amend the wording of the client storage agreements and consent forms, to ensure that informed consent is obtained. In the cord blood/tissue storage agreement there is a statement that 'no assurance or guarantee can be made about the effectiveness of preservation

		nor the benefits or utility derived from it'. This broad disclaimer does not differentiate between clinical effectiveness and assurances regarding the outcome of processing and storage; the limits of the latter should be validated and defined by the establishment. The DI is advised to consider the wording that is in client information and the client storage agreement, to reflect the level of processing that UCT undergoes. It is not apparent that processing of UCT undertaken by the establishment, serves only to cryopreserve the tissue as a whole, rather than to isolate cells prior to cryopreservation. For example, references made to processing or storage of 'cord tissue stem cells' and the use of the phrase in the client storage agreement 'cells present in the cord tissue will only be stored and will not be further analysed for quality or quantity' could imply that stem cells are isolated from tissue at some point during UCT processing. The option to withdraw consent in the client consent form is ambiguous and it is currently unclear that the client can withdraw from the agreement at any time, including following procurement. The DI is also advised to amend the maternal health questionnaire which incorrectly refers to HLTV I rather than HTLV I.
3.	GQ1i GQ6b	The DI is advised to amend the wording of the storage location on the computerised record to reflect the nomenclature in the Cryogenic Storage SOP BS008, as the currently used quarantine terminology is inaccurate.
4.	GQ1q, GQ2a	The establishment has agreements in place with a number of other organisations and these are regarded as 'enduring'. The DI is advised to incorporate TPAs and SLAs into a quality management system to ensure that they are reviewed and updated on a regular basis.
5.	GQ2b	The DI is advised to carry out a systematic audit of policies and procedures to ensure that policies and patient information relating to cell and tissue processing and storage reflect current practices.
6.	GQ7a	The DI is advised to provide guidance to all staff regarding examples of what does / does not constitute a Serious Adverse Event or Serious Adverse Reaction.
7.	PFE1a	Currently the Grade A cabinet, where UCT processing is carried out, is located in the room where cryopreservation occurs. The DI is advised to conduct a risk assessment of the area where UCT processing occurs to address the risk to tissue and cells, as well as the risks to staff carrying out the work.
8.	PFE1f	The DI is advised to approach the establishment's scientific advisor for expert advice when addressing the validation of practices and processes. Refer to the shortfall against Standard GQ2d for further details.
9.	PFE2b	The DI is advised to review the scope of environmental monitoring that is currently carried out in the processing area and in the background environment, with particular reference to the variety of settle plates used in each location (for example, by introducing Sabouraud agar plates into the current environmental monitoring schedule in addition to the plates that are currently used).
10.	PFE3a	The DI is advised to risk asses the system of rack based versus aliquot labelling system used for PBS storage, especially if other reagents were to be introduced

		that could be stored in this manner which could lead to reagents in unlabelled tubes being mixed up.
11.	PFE3c	Freezer alarm systems are tested on a six monthly basis by the maintenance company. The DI is advised to consider increasing the frequency of these tests to ensure appropriate monitoring arrangements are in place.

Concluding comments

There were areas of good practice seen during the inspection. The DI has undertaken a proactive approach to maintaining relationships with the establishment's international partners and has introduced monthly summary reports. Furthermore, a comprehensive induction programme is in place for staff involved in sample processing, as well as a competency based training matrix.

A range of risk assessments has been carried out by the establishment, encompassing health and safety and regulatory issues; advice has been issued to the DI regarding further risk assessments that could be carried out for processing areas. Additionally, a colour coding system for reagents has been introduced so that stock rotation is maintained.

Since the last inspection, the base level of contamination present in UCT samples and the processes in place to reduce this, have both been evaluated. Further action is required from the establishment to ensure that that any potential bioburden and risk of sample cross contamination is recognised. Major shortfalls relating to this were found against standards GQ1b, PFE2b and PFE3a and are detailed above within the summary of inspection findings.

In total, four major shortfalls were found. These relate to document control with respect to policies reflecting practice and validation of processes affecting the quality and safety of tissues and cells (including transportation). Seven minor shortfalls were found relating to informed consent, independent audits, HTLV-1 testing, adverse event reporting, concessional release procedures and monitoring of freezers out of hours, where policies should reflect current practice.

The HTA has also given advice to the DI with respect to other points relating to informed consent, governance and quality issues and premises, facilities and equipment.

The HTA requires that the DI addresses the 12 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 June 2013

Report returned from DI: 18 June 2013

Final report issued: 28 June 2013

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: 30 January 2017

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

Consent

Standard
C1 Consent is obtained in accordance with the requirements of the HT Act 2004, the Human Tissue (Quality and Safety for Human Application) Regulations 2007 and as set out in the HTA's Codes of Practice.
a) If the establishment acts as a procurer of tissues and / or cells, there is an established process for acquiring donor consent which meets the requirements of the HT Act 2004 the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (Q&S Regulations) and the HTA's Codes of Practice
b) If there is a third party procuring tissues and / or cells on behalf of the establishment the third party agreement ensures that consent is obtained in accordance with the requirements of the HT Act 2004, the Q&S Regulations and the HTA's Codes of Practice.
c) The establishment or the third party's procedure on obtaining donor consent includes how potential donors are identified and who is able to take consent.
d) Consent forms comply with the HTA Codes of Practice.
e) Completed consent forms are included in records and are made accessible to those using or releasing tissue and / or cells for a Scheduled Purpose.
C2 Information about the consent process is provided and in a variety of formats.
a) The procedure on obtaining consent details what information will be provided to donors. As a minimum, the information specified by Directions 003/2010 is included.
b) If third parties act as procurers of tissues and / or cells, the third party agreement details what information will be provided to donors. As a minimum, the information specified by Directions 003/2010 is included.
c) Information is available in suitable formats and there is access to independent interpreters when required.
d) There are procedures to ensure that information is provided to the donor or donor's family by trained personnel.
C3 Staff involved in seeking consent receive training and support in the implications and essential requirements of taking consent.
a) Staff involved in obtaining consent are provided with training on how to take informed consent in accordance with the requirements of the HT Act 2004 and Code of Practice on Consent.
b) Training records are kept demonstrating attendance at training on consent.

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.
e) There are procedures for tissue and / or cell procurement, which ensure the safety of living donors.
f) There are procedures for tissue and / or cell procurement, which ensure the dignity of deceased donors.
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.
n) The establishment ensures imports from non EEA states meet the standards of quality and safety set out in Directions 003/2010.
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.
c) In cases other than autologous donors, donor selection is carried out by authorised personnel and signed and reviewed by a qualified health professional.
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.
f) Samples taken for donor testing are clearly labelled with the time and place the sample was taken and a unique donor identification code.
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.

d) Where appropriate, there are procedures to ensure that the premises are of a standard that ensures the dignity of deceased persons.
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.