Site visit inspection report on performance against HTA quality standards

Future Health Technologies Ltd
HTA Licensing number 22503

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, and the**

- **storage of relevant material which has come from a human body for use for a scheduled purpose other than transplantation under the Human Tissue Act 2004**

30 November & 1 December 2011

Executive Summary

A site visit inspection of Future Health Technologies Ltd (the establishment) was carried out by the HTA on 30 November & 1 December 2011.

The establishment was found to meet the majority of the HTA standards across the four areas of: consent; governance and quality; premises, facilities and equipment and disposal. Shortfalls were found in each of the four categories.

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

All 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

Future Health Technologies Limited (FHT) is a commercial tissue bank who are responsible for the procurement, processing and storage of umbilical cord blood (UCB) and umbilical cord tissue (UCT) under the HTA licence. UCB and UCT are stored for autologous or allogeneic family use for potential future stem cell treatments.

FHT have recently offered a new service that includes the processing and storage of stem cells extracted from dental pulp. This variation to the establishments HTA licence was approved prior to a site-visit inspection, based on the establishment's validation report and associated documents that were submitted for desk-based review.

The establishment also carry out their own virology testing (serology and PCR / NAT testing) which follows an application to vary their licence and bring this activity in-house earlier this year. In order to approve commencement of virology testing the HTA conducted a focussed, non-routine inspection in April 2011. This inspection was conducted by an HTA inspection team and a specialist advisor who provided expert knowledge of donor serology testing.

Umbilical cord blood is processed using a closed system designed not to permit environmental exposure. This is carried out in an unclassified environment. Cryoprotectant is dispensed in a class II microbiological cabinet and addition of the cryoprotectant also takes place in the cabinet, introduced via a sterile filter.

Processing of umbilical cord tissue and dental pulp take place in the establishment's clean room suite. Each activity takes place in a separate, dedicated clean room and umbilical cord tissue and dental pulp are both processed in grade A cabinets situated in clean rooms maintaining grade C background air quality. Continuous particle monitoring is carried out in the grade A cabinets and sessional environmental monitoring is carried for all processing activities.

This report relates to a routine inspection of the activities and premises of FHT under HTA's standards as defined by the Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment (The Guide) and is the third routine inspection of the Human Application Licence 22503. The establishment have previously been inspected in November 2007 and September 2009.

This was a coordinated inspection, carried out in conjunction with an inspection team from the Medicines and Healthcare products Regulatory Agency (MHRA). FHT hold a Blood Establishment Authorisation from the MHRA and as such, were inspected against standards outlined in the Blood Safety and Quality Regulations 2005. The timetable for this joint inspection was developed following discussion between HTA and MHRA inspectors and was shared with the establishment prior to the inspection.

In response to the findings of the routine inspection carried out on 30 November and 1 December 2011 the HTA conducted an additional non routine inspection on 9 January 2012. This was a half day inspection and centred around gathering information relating to the shortfall outlined under GQ5 (b). As a consequence of this shortfall the HTA issued Directions on 23 January 2012 relating to the storage and management of stem cell products for clients whose donor serology testing did not meet the mandatory requirements outlined in Annex B of the Guide, at the time of donation.

Meeting the HTA's licensing standards

The HTA developed its licensing standards with input from its stakeholders, in order to ensure the safe and ethical use of human tissue. The HTA expects licensed establishments to meet these standards.

This is an exception-based report: only those standards that have been assessed as not met are included. Where the HTA determines that a licensing standard is not met, the level of the shortfall will be classified as 'Critical', 'Major' or 'Minor' (see Appendix 3: Classification of the level of shortfall).

Unless otherwise advised, the establishment is required to inform the HTA within 14 days of the receipt of the final report of the corrective and preventative actions that will be taken to ensure that the improvements are addressed. A template for this purpose is provided as a separate Word document.

Please see Appendix 2: Human Application standards, to view all human application standards. Standards which do not apply to this licence are highlighted in Appendix 2.

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.		
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, the Q&S Regulations and the HTA's Codes of Practice.	The inspection team observed that it has previously been established practice to send out kits for collection of UCB and UCT at the same time - irrespective of whether consent has been obtained for UCB and UCT or UCB alone. This has promoted the collection of UCT in conjunction with UCB in the majority of procurements. In these cases UCT has been processed and stored at FHT and several are now marked for disposal because the client did not wish for the cord tissue to be procured, processed or stored. The consent form for the procurement of UCB and UCT requires amendment to make explicit consent for blood, tissue or both. The kits for collection of UCT should only be sent out to the health care professional (HCP) in situations where consent has been given for collection of umbilical cord tissue. The HCP should be made aware that the consent forms are to be amended and that in the interim UCT should only be collected when explicit consent is in place. *Since the time of the inspection the DI has advised that kits for collection of umbilical cord tissue will only be sent out when consent is specifically given.*	**Major**

d) Consent forms comply with the HTA's Codes of Practice.	A number of issues were noted with the consent form: 'Mothers Informed Consent Form and Stem Cell Storage Agreement'. This form is currently in use for obtaining consent for procurement, processing and storage of UCB and/or UCT and also virology testing of maternal blood. The Mother's Informed Consent Declaration does not make explicitly clear whether consent is being given for collection of UCB only, UCT only or both. This has led to multiple situations where cord tissue is collected, processed and stored without consent. (see C1b) Page one of the consent booklet titled 'mothers informed consent declaration' was duplicated and accompanied tissues providing consent for receipt of UCB and / or UCT for processing and storage in most cases. In these situations the booklet of information is returned at a later date. It was noted on inspection that different versions of this document were in use (the Italian and Portuguese versions provided had a translated copy in English that contained different information with respect to how virology testing would be carried out). Both versions were denoted with the same version number. The 'Mother's Informed Consent Declaration' should also make clear that in utero collection of UCB is not in accordance with the guidelines from the Royal College of Obstetrics and Gynaecology (RCOG). The declaration also states that maternal blood samples will be tested in accordance with the Human Tissue Act instead of the Human Tissue (Quality and Safety for Human Application) Regulations 2007. Page 5 of the 'Stem Cell Storage Agreement' entitled 'Required maternal blood test schedule' outlines potential transmission of disease to the child and states '....if transmitted would render the stem cells unsuitable for storage'. The establishment conducts mandatory virology testing on the maternal blood sample (in accordance with Annex B of 'The Guide') and should therefore remove the reference of disease transmission to the child.	**Major**

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.		
g) There are procedures to ensure that an authorised person verifies that tissues and / or cells received by the establishment meet required specifications.	Written procedures did exist but the establishment had accepted a number of tissues for processing and storage that did not meet required specifications. The inspection team noted the following: - umbilical cord tissue was accepted for processing and storage with inadequate consent. - Teeth have been accepted for processing and storage of stem cells with either inadequate or absent serology testing. - Cord blood was accepted for processing and storage when testing of maternal blood was carried out by a laboratory in Spain with whom FHT has no agreement in place or assurance that the testing is conducted in accordance with HTA standards. The establishment staff should review their current receipt and acceptance criteria and ensure that tissues / cells that do not fulfil mandatory requirements are not accepted for processing and storage.	**Major**
n) The establishment ensures imports from non-EEA states meet the standards of quality and safety set out in Directions 003/2010.	*A number of the identified shortfalls outlined in this report are applicable to imported tissues / cells.* *FHT must ensure that corrective and preventative actions address any shortfalls indentified for both UK procured and imported tissues / cells accepted for processing and storage.*	
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.	FHT currently advises potential donors and their guardians, that teeth may be extracted by dentists in order to provide stem cells for extraction, processing and storage. At the time of inspection the establishment did not have any third party agreements in place with dentists who were procuring teeth for this purpose.	**Major**

r) Third party agreements specify the responsibilities of the third party and meet the requirements set out in Directions 003/2010.	A number of TPAs viewed on inspection were generic, not version controlled and required review. The TPAs are not fit for purpose as they do not specify the requirements of the guide (page 42; paragraph 188 – 202). The establishment have an up to date TPA in place with a CPA accredited testing laboratory for confirmatory retesting of any maternal blood samples that tested positive using in-house serology and PCR testing. An audit of the third party premises had recently been carried out but a number of critical processes were not assessed as part of the audit. The DI had recognised that this was a shortfall and intends to reaudit the testing facility in the very near future.	**Major**

GQ2 There is a documented system of quality management and audit.		
b) There is an internal audit system for all licensable activities.	The establishment conducts a review of written SOPs in order to capture any required amendments on an annual basis. At the time of inspection the establishment did not conduct any procedural audits in order to assess whether staff are carrying out licensed activities in accordance with written standard operating procedures. This was particularly pertinent during the inspection of the clean room facilities when staff were observed, on a number of occasions, carrying out activities that were not in accordance with the establishment's written procedures. The DI assured the inspection team that plans were in place to include audits of staff members performing procedures early next year. The DI conducts a regular audit of client files (six per calendar month) and the inspection team considered this to be good practice. The DI does not currently document any nonconformities that are discovered as a result of these audits. Documenting the non conformities will provide an opportunity to trend results and highlight any actions that are required. *Since the time of the inspection the establishment have advised that procedural audits are carried out on a weekly basis and the procedure for auditing client files instructs documenting any non conformities.*	**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.	The establishment have carried out a number of extensive validation studies and the inspection team recognised studies have been carried out with scientific rationale. However the inspection team noted that additional, more detailed validation was required. Validation needs to be set up for long term storage of dental pulp cells. There are currently no limits defined for acceptance of cell loss resulting from processing and storage. The Tooth Stem Cell Storage Agreement refers to 'insufficient dental pulp' and 'low vitality / cell count' but no actual limits are defined. It was observed that the temperature validation protocol was written after the results had been generated. There were a number of instances where the operating practice at the time of inspection did not reflect that of conditions of the validation studies. - At the time of the HTA inspection, dissection and cryopreservation of cord tissue was carried out using cell-gro media that had been aliquotted and stored at minus 20^{o}C. It was noted that the validation studies for cryopreservation had used fresh cell-gro media. The establishment should consider whether the use of a diluted solution of cell-gro medium that has been subjected to a freeze-thaw cycle will yield results that are different to those obtained in the original validation studies. - The operator processing umbilical cord tissue was observed to keep excess tissue overnight 'just in case' it was required. However there was no mention of this practice in the relevant SOP or validation studies and hence no consideration of what effect storage of this tissue in the fridge overnight may have on the cell properties.	**Major**

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.	The establishment do not currently consider whether a donor has received fluids or received donated blood prior to providing a blood sample for mandatory serology / NAT testing. This information should be provided by the donor and if appropriate, the establishment should apply a haemodilution algorithm in accordance with Annex B, 2.3 to ensure that results of serology / NAT tests are valid.	**Major**
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.	Collection kits for teeth were distributed prior to HTA approval of a licence variation to process and store stem cells extracted from dental pulp. The kits, which were sent outside of the EU, contained blood spot cards that are not CE marked. The HTA provided explicit instruction to FHT that testing of blood collected on blood spot cards did not fulfil the mandatory testing requirements outlined in Annex B – Laboratory tests required for donors, and should not be used until such time as the blood spot cards obtain a CE mark. During the inspection it was noted that the establishment had accepted, for processing and storage, 18 teeth where the donor blood sample had been provided on a blood spot card, three teeth had been accepted from donors that did not have any associated donor blood sample and one tooth had been accepted when no associated serology tests had been carried out at the time of donation. **HTA Directions (dated 23 January 2012) have been issued in relation to the shortfall identified against this standard.**	**Major**
c) In cases other than autologous donors, donor selection is carried out by authorised personnel and signed and reviewed by a qualified health professional.	The consent forms state that tissues will be 'privately stored for future autologous use or family allogeneic medical application'. The establishment should consider that if stem cells are to be released for potential allogeneic use, the selection criteria for donors will need to be in accordance with Annex A of The Guide, 2.2 Allogeneic living donor. The questions asked for donor medical history should therefore be reviewed and amended appropriately.	**Minor**

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.	The current procedure is that administration assistants will review the donor's medical history and the inspection team were advised that assistants would ask for additional information if required. There was no procedure in place documenting what were acceptable criteria.	**Major**
e) Testing of donor samples is carried out using CE marked diagnostic tests.	The establishment have received, processed and stored stem cells from dental pulp from a number of donors who have provided blood samples for virology testing on a blood spot card that is not a CE marked diagnostic kit. (See GQ5b).	**Major**
f) Samples taken for donor testing are clearly labelled with the time and place the sample was taken and a unique donor identification code.	Maternal blood samples are not currently labelled with the time, date and place of collection. *Since the time the inspection labels now include all mandatory information.*	**Minor**
GQ7 There are systems to ensure that all adverse events are investigated promptly.		
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.	The establishment had set defined thresholds for transport temperatures but need to consider what actions will be taken when cells / tissues have been outside of the temperature specifications in order to provide assurance that cells have not been adversely affected. One of the client files viewed as part of the audit trail showed that tissues had been outside of the required range for a number of hours before receipt, but any potential consequences of this did not appear to have been considered.	**Minor**

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.	FHT had supplied kits containing blood spot cards to an agent in a country outside of the EU prior to receiving approval for the use of blood spot cards in mandatory serology testing. The HTA subsequently notified FHT that the cards were not CE marked and could not be used. FHT failed to implement a recall procedure or notify the agent that the blood spot cards should not be used for three months following notification from the HTA. Of the twenty kits that had been supplied – 18 were returned with used blood spot cards, and tissues were accepted for processing and storage. Two of the kits had been used for demonstration purposes. The inspection team had serious concerns about the establishment's willingness to recall the products, despite written notification that the blood spot cards did not comply with the HTA's donor testing requirements. The reason provided for not initiating a recall of products was that the kits had been allocated to clients who did not wish to use an alternative method of blood collection (See also GQ5b).	**Major**

Premises, Facilities and Equipment

Standard	Inspection findings	Level of shortfall
c) There are procedures for cleaning and decontamination.	The transport canisters used to transport tissue from the point of procurement to the establishment for processing and storage are reused. The current decontamination procedure is to wash the transport canisters in a dedicated dishwasher. The inspection team did not consider this was an appropriate method to ensure decontamination of the canisters and require the establishment to implement a recognised method of viral inactivation in order to ensure safe reuse of the canisters.	**Major**
	During the visual inspection of the clean room it was observed that no cleaning of the class A cabinet took place between handling of dental pulp stem cells from different clients. The requirement for a clean down of the hood was stated in the SOP but the inspection team considered that the SOP should be updated to be more specific /detailed and staff should be made aware of any changes. Cord tissue samples from multiple donors were also observed being processed in the class A cabinet simultaneously with no clean down between donors.	**Major**

Disposal

Standard	Inspection findings	Level of shortfall
D1 There is a clear and sensitive policy for disposing of human body parts and tissues.		
a) The disposal policy complies with HTA's Codes of Practice.	There are a significant number of samples that are earmarked for disposal that have not been disposed of due to time constraints. The DI is advised to coordinate the disposal of these samples without delay.	**Minor**

Advice

Below are matters which the HTA advises the DI to consider.

No.	Standard	Advice
1.	C1	The establishment currently display the HTA logo on the front of consent forms and the side of collection kit boxes. The inspection team raised a concern that the use of the logo appears as an endorsement of the company and ask that the establishment remove the HTA logo from its collection packaging and literature.
2.	GQ1(l)	The establishment had a contingency agreement in place with another HTA licensed establishment but this was in draft form. The DI is advised to finalise and implement this agreement without delay.
3.	GQ6(a)	The potential risk of a mix up when two cord blood samples are procured from non-identical twins was considered during the inspection. The establishment is advised to consider any appropriate measures that could be implemented in order to mitigate this risk (such as providing additional bar code labels for the blood bags).
4.	GQ7(c)	The procedure for identification and reporting of serious adverse events and reactions does not include a named deputy who will report to the HTA in the DI's absence.
5.	GQ7(d)	The DI is advised to ensure that non conformances are appropriately followed up and accompanying paperwork is filed in client files to indicate when a non conformance has been detected.
6.	PFE5(c)	The DI is advised to consider the type and amount of equipment in the grade C clean room and limit to essential materials appropriate for the required air quality of the room. The DI is also advised to ensure that the interim measure to repair a defect in pressures in the clean room is rectified using appropriate materials.
7.		The DI is advised that culturing of dental pulp stem cells in a T25 flask and passage into a T75 flask would be appropriate in order to provide greater numbers of cells for use in long term storage / other validation studies. Passage into a T75 flask could be carried out as processing under FHT HTA licence.

Concluding comments

FHT Limited have expanded their activities significantly since the requirement for an HTA Human Application licence and now offer processing and storage for a number of different tissue types and also undertake their own serology and microbiology testing. The HTA inspection team recognised that FHT have conducted some validation studies to provide assurance of processing protocols and have also made progress against areas where shortfalls were previously identified.

Report sent to DI for factual accuracy: 23 January 2012

Report returned from DI: 6 February 2012

Final report issued: 12 March 2012

Appendices

Appendix 1: HTA inspection process

The Human Tissue Authority (HTA) regulates the removal, storage, and use of human bodies, body parts, organs and tissue for activities such as research, transplantation, and education and training. The legal requirements for establishments which carry out such activities are set out in the Human Tissue Act 2004 and The Human Tissue Act 2004 (Ethical Approval, Exceptions from Licensing and Supply of Information about Transplants) Regulations 2006.

The HTA is also the designated Competent Authority for the purposes of the European Union Tissue and Cells Directives (the Directives) so far as they relate to tissues and cells for use in human application (using tissues and cells for patient treatment). On 5 July 2007 the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (the Regulations) came into force. The Regulations formally transposed the Directives into UK law. Under the Regulations the HTA regulates and licences the procurement, testing, processing, storage, distribution, import or export of tissues or cells intended for human application. The HTA has produced detailed Directions to complement the implementation of the Directives.

As part of the regulatory framework, the HTA licenses establishments and undertakes inspections to assess compliance with expected standards.

Inspections

We use the term 'inspection' to describe when we:

- visit an establishment to meet with staff, view premises and facilities, and review policies and procedures (a site-visit inspection); or
- assess written information we have requested from an establishment (a desk-based assessment / inspection).

We carry out inspections to assess if the Designated Individual (DI) is suitable to supervise the activity covered by the licence, as it is their responsibility to ensure that:

- other staff working under the licence are suitable;
- suitable practices are used when carrying out the activity;
- the conditions of the licence are met;
- the conditions of third party agreements are met; and
- the information and confidentiality requirements set down in the Regulations are complied with.

We also need to be satisfied that the licence applicant or holder, the establishment's premises, and the practices relating to licensed activities, are suitable.

To help us reach our decisions, we have developed standards under four headings: Consent; Governance and Quality; Premises, Facilities and Equipment; and Disposal.

After every site visit inspection, we write a report documenting our findings. Where we find a particular standard is not fully met, we will describe the level of the shortfall as 'Critical', 'Major' or 'Minor'. In most cases, it will be the responsibility of the DI to seek the HTA's agreement on how they will address the identified shortfalls. More information about the classification of shortfalls can be found in Appendix 3.

The majority of our site-visit inspections are announced. If we have concerns about an establishment, we can also undertake an unannounced site visit inspection.

You can find reports for site visit inspections which took place after 1 November 2010 on our website.

Appendix 2: HTA Standards

Standards which are not applicable to this establishment have been highlighted.

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

   or

   A number of 'major' shortfalls, which individually do not pose a direct risk of harm to a recipient or living donor, 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 or 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/or cells.

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 at the time of the next inspection.

Follow up actions

A template corrective and preventative action plan is available as a separate Word document. 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.