Site visit inspection report on performance against HTA quality standards
Altrika Ltd
HTA licensing number 11020

Licensed for the

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

13 October 2011

Executive Summary

A site visit inspection of Altrika Ltd (the establishment) was carried out by the HTA on 13 October 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. Some shortfalls were found, particularly in relation to governance and quality systems; and to premises, facilities and equipment. Two critical shortfalls were found relating to the validation of the process, reagents and quality control testing used in the preparation of one type of cell.

Any particular examples of strengths or good practice are included in the concluding comments section of the report.

The inspection focused on the processing of Blastomere Like Stem Cells, which was added to the cell types included in the licence for the establishment in May 2011. Activities undertaken in respect of other cell types included in the licence were reviewed more briefly.

Notwithstanding the shortfalls identified on inspection, overall the HTA found 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

The establishment has been licensed by the HTA since August 2006, originally under the name CellTran Ltd, subsequently under the name York Pharma, and as Altrika Ltd, which is an operating company within Ilika Technologies Ltd, since November 2009. The establishment currently produces three products:

Cryoskin® is an ATMP, produced from a human cell bank, and is regulated by the Medicines and Healthcare products Regulatory Agency (MHRA).

Myskin® is an autologous product, prepared by growing keratinocytes in culture from a biopsy sample procured in a hospital from a patient with severe burns. The keratinocytes in the biopsy sample are expanded in culture and seeded on a flexible silicone sheet or delivered as a cell suspension in phosphate buffered saline. The cultured cells are returned to the hospital and applied to the burn or other non-healing wound, where they can initiate healing

Oristem® is a new product, which is processed by Altrika Ltd as part of a consortium of three HTA-licensed establishments. Blood is procured from clients by one of these establishments, transferred to Altrika Ltd for testing, processing and short-term storage, and then transferred to the third establishment for long-term storage. The technology relating to the preparation of this product has been licensed from a company in the USA by the establishment responsible for the procurement and distribution of the blood cells.

The establishment does not undertake the following activities under HTA licence 11020: import or export.

The HTA has conducted two previous site visit inspections; the first took place in January 2008. A joint inspection of Altrika Ltd was carried out by the HTA and MHRA in February 2010; this reviewed all aspects of the licences relating to Cryoskin® and Myskin®. Following the latter inspection, the HTA considered placing additional conditions on the establishment's licence, but did not do so, as the areas of concern were addressed before the final inspection report was issued.

The site visit inspection of the establishment on 13 October 2011, which was carried out under the Human Tissue (Quality and Safety for Human Application) Regulations 2007, focused on the preparation of the new Oristem® product, following the addition of this product to the licence in May 2011. The process involves the extraction and cryopreservation of a class of cells termed Blastomere Like Stem Cells (BLSCs) from adult peripheral blood. Prior to the inspection, at the request of the HTA, the establishment had completed a Preparation Process Dossier (PPD) giving details of the processing of BLSCs. During the inspection, the HTA team interviewed several members of staff, conducted a visual inspection of the premises, reviewed documents relevant to activities carried out under the licence, and held a round table discussion relating to the PPD.

During a recent inspection of the establishment responsible for the procurement of blood for the preparation of BLSCs, an audit trail of traceability was undertaken for the procurement and distribution of five donations. The audit trail was continued at Altrika Ltd, where the testing and processing records for all five donations were reviewed. All processing records were complete and no anomalies were observed. Four testing records were complete, and indicated negative serology results for all mandatory tests. It was noted that Altrika Ltd does not receive copies of consent documentation or information relating to the donor's medical and behavioural history; any requirement for additional serology testing is therefore dependent upon this being requested by the establishment responsible for procurement. The cryopreserved BLSCs from two donations were observed in the -80°C quarantine freezer at Altrika Ltd, including one donation forming part of the audit trail; in both cases, technical anomalies in the blood samples provided for serology had prevented this testing being undertaken. It is planned that repeat samples for serology testing will be obtained from the

donors, but these samples will not conform to the requirement in Annex B of the HTA Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment that samples for serological testing 'must be obtained at the time of donation or, if not possible, within seven days post donation'.

After considering the lack of validation of the process for the extraction and cryopreservation of the BLSCs and the incomplete characterisation of the solutions used in the process, the HTA concluded that there was insufficient evidence to confirm that the process does not render the cells either clinically ineffective or harmful. This represents a critical shortfall since it poses a significant direct risk of causing harm to a recipient patient. In order to address the situation, the HTA convened a Regulatory Action Panel (RAP) to consider what regulatory action should be taken. The outcome of the RAP was the issue of Directions to ensure that all processing of blood to isolate BLSCs for human application is suspended immediately, and that any samples of BLSCs which have been prepared and cryopreserved are quarantined with immediate effect and not released to any individual without prior written permission from the HTA.

The processing of keratinocytes, including changes made subsequent to the joint inspection by HTA and MHRA, was reviewed briefly during this site visit inspection. This process was found to meet the majority of the HTA standards, with two minor shortfalls in relation to premises, facilities and equipment. It was noted that the establishment had acted on the advice relating to improvements to the documentation system and practices which had been given during the previous inspection.

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

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.		
b) There are procedures for all licensable activities that ensure integrity of tissue and / or cells and minimise the risk of contamination.	Some Standard Operating Procedures relating to the processing of BLSCs are in draft format; others include minor errors and inconsistencies. There is no procedure for dividing incoming solutions into aliquots and assigning an expiry date to such aliquots.	**Minor**
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.	The reagents used to process the BLSCs have not been defined, and there is no assurance that they are appropriate for clinical or medical use. In particular: The components of the clarification solution have not been disclosed to the DI; The cryopreservation solution contains a high concentration of Dimethyl Sulfoxide (DMSO) which is not of an appropriate grade for clinical use. The reagents used to process samples of BLSCs were not released for use in accordance with the standard Quality Control procedures at the establishment. The shortfall under standard GQ1j is also applicable to standards GQ4j and PFE5j.	**Critical**
GQ2 There is a documented system of quality management and audit.		
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 process used to isolate BLSCs from adult peripheral blood has not been validated and there is no assurance that it can achieve consistent or appropriate results. The quality control testing of the cells gives no assurance that the cells are viable or have any of the properties required for their utility; the microbiological testing is inappropriate. Therefore, there is insufficient evidence to confirm that the process does not render the cells either clinically ineffective or harmful.	**Critical**

GQ4 There is a systematic and planned approach to the management of records.		
j) Records are kept of products and material coming into contact with the tissues and / or cells.	The records of the reagents coming into contact with the BLSCs are incomplete as the composition of the clarification solution is not known. (See standard GQ1j).	
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.	The process for the isolation of BLSCs cannot be risk assessed because there is insufficient evidence to confirm that the process does not render the cells either clinically ineffective or harmful.	**Major**

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.	Air particle counting is not carried out during routine processing of keratinocytes or BLSCs in the Class A cabinets. The current European Guide to Good Manufacturing Practice (GMP), Annex 1 of Directive 2003/94/EC, clearly indicates that air particle monitoring should be undertaken for the full duration of critical processing. The establishment has conducted trials of suitable air particle counters during processing operations, with successful results. The establishment has placed an order for particle counters.	**Minor**
c) There are procedures for cleaning and decontamination.	The incubators in the clean room are cleaned following the processing of each sample of keratinocytes. The requirement for the cleaning to be carried out is not included in the relevant Standard Operating Procedure.	**Minor**

PFE3 There are appropriate facilities for the storage of bodies, body parts, tissues, cells, consumables and records.		
d) There is a documented, specified maximum storage period for tissues and / or cells.	The maximum safe storage time for the peripheral blood prior to processing to extract BLSCs has not been determined.	**Minor**
PFE5 Equipment is appropriate for use, maintained, quality assured, validated and where appropriate monitored.		
j) For each critical process, the materials, equipment and personnel are identified and documented.	The materials used for the processing of BLSCs are not fully identified and documented as the composition of the clarification solution is not known. (See standard GQ1j).	

Advice

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

No.	Standard	Advice
1.		The HTA advises the DI to liaise with the DI at the establishment responsible for the procurement of blood for the preparation of BLSCs, to ensure that sufficient information is provided to permit the completion of the PPD, and the validation of the process. This may include information from the company in the USA which has licensed the process to that establishment.
2.		The HTA advises the DI to review the status of the BLSCs held in storage at the establishment as a consequence of the serological testing of the donors being unsatisfactory. Any replacement blood samples provided by the donors for repeat testing will not meet the requirement that samples for serological testing 'must be obtained at the time of donation or, if not possible, within seven days post donation'.
3.	GQ5b	The HTA advises the DI to liaise with the DI at the establishment responsible for the procurement of blood for the preparation of BLSCs, to ensure that, where appropriate, additional serological tests are carried out.
4.	PFE1	The HTA advises the DI to review the equipment present in the cleanroom, and to remove any items which are not essential for processing.
5.	PFE3c, PFE5c	The HTA advises the DI to introduce a schedule of testing for the temperature alarms on the incubators, refrigerators and freezers.
6.	PFE5	The HTA advises the DI to review the reports from external maintenance companies, to check that the correct units are included for refrigerator and freezer temperatures. The HTA also advises the DI to document these reviews and any corrective actions undertaken.

Concluding comments

The HTA is satisfied that the establishment is suitable to be licensed for the procurement, testing, processing, storage and distribution of human tissues and cells for human application under the Human Tissue (Quality and Safety for Human Application) Regulations 2007.

Examples of effective practices which were observed during the inspection include the consistent use of a unique code number to identify samples for BLSC preparation at all three establishments involved in different stages of this activity. At Altrika Ltd, a good risk assessment of the processing of multiple cell types and the requirement for suitable segregation has been undertaken. In addition, improvements have been made to the processing of keratinocytes since the previous inspection; this includes modifications and improvements to the cleanroom where the processing of both keratinocytes and BLSCs is carried out.

Report sent to DI for factual accuracy: 02 November 2011

Report returned from DI: 16 November 2011

Final report issued: 01 December 2011

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: 03 July 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 any of the activities undertaken at 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.