Site visit inspection report on compliance with HTA minimum standards

NuVision Biotherapies Ltd

HTA licensing number 22656

Licensed for the

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

12-13 June 2018

Summary of inspection findings

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

Although the HTA found that NuVision Biotherapies Ltd (the establishment) had met the majority of the HTA standards, two major shortfalls and fifteen minor shortfalls were found in relation to 'Consent', 'Governance and Quality Systems' and 'Premises, Facilities and Equipment'.

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.

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

Tissue Category; Tissue Type	Procurement	Processing	Testing	Storage	Distribution	Import	Export
Membrane, Amniotic; Amniotic Membrane	**E/TPA**	**E**	**E**	**E**	**E**		**E**

Background to the establishment and description of inspection activities undertaken

The establishment specialises in the production of a vacuum-dried amnion-derived product called Omnigen, which can be stored at temperatures between 0 to 25ºC for up to a year. This is the second HTA inspection of the establishment since it was granted a HTA licence in 2015. A follow up visit took place in March 2017 to assess progress towards meeting agreed CAPA actions.

The amniotic membrane used for the manufacture of Omnigen is procured from donors undergoing elective caesarean sections at a nearby hospital. Donor medical history is first evaluated by a Research Midwife at the hospital, working under a third party agreement with the establishment, to assess donor suitability prior to the donor being approached for consent. Consent for the donation is obtained either by the Research Midwife or trained staff from the establishment who hold honorary hospital contracts. The removal of the amniotic sac is performed by the same staff member responsible for obtaining consent. Once harvested, the amniotic membrane is double-bagged in sterile saline and transported in labelled boxes back to the establishment for processing.

Blood samples for mandatory serological testing are obtained at the time of tissue donation. Staff who obtain consent are also responsible for ensuring the blood samples are delivered to the pathology testing laboratory at the hospital.

Until recently, aliquots of the antibiotic cocktail used to reduce the bioburden of the tissue during processing were stored in a -80ºC freezer at the 'Academic Ophtalmology' research department within the hospital. Staff would collect a single vial of antibiotics from the research department and transport both the tissue and antibiotics to the processing facility within a defined time frame. On the day before the inspection, the antibiotics had been moved from the hospital to a dedicated -20ºC freezer within the establishment's storage facility. The freezer is temperature-monitored by a probe linked to a wireless internet connection for call outs to staff members in the event of a temperature deviation.

Processing of the amniotic membrane is performed within a dedicated isolator located within a Grade D background. Prior to processing, staff prepare kits containing all the necessary consumables required during a single manufacturing session. A small stock of the kits are stored within the Grade D room in a stock cabinet for easy access. Processed Omnigen awaiting donor serology results and microbiological sterility tests are stored on separate shelves in a quarantine cabinet in the clean room until cleared for release. The Omnigen products are then transferred to a temperature-monitored stock cupboard, located in the office, where they are organised into different boxes based on size. Sales staff are responsible for packing the Omnigen for release to end users. Omnigen products intended for clinical trials are stored separately to ensure the requested numbers of products are available. Omnigen products which do not meet the criteria for release are labelled for research only and stored in a separate cabinet.

The inspection included round table discussions with the DI, Chief Executive Officer, Operations Manager, Product Manager and the Marketing Director. The visual inspection included a inspection of the clean room facility, consumable and reagent storage room, staff offices, the testing laboratory and the storage freezer in the research department at the hospital. An audit of records was performed looking at donor consent and serology testing, processing records and environmental monitoring records of two Omnigen products – one intended for clinical use, and another intended for research purposes. There were minor discrepancies in one processing record relating to consistency of record keeping.

The establishment is also licensed for storage of relevant material from a human body for use for a scheduled purpose. This aspect of the licence was not inspected during this visit.

Inspection findings

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

Compliance with HTA standards

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

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.	The medical history questionnaire is not sufficiently detailed to exclude the risk of infectious diseases based on donor travel history and country of origin. The donor exclusion criteria on the consent form does not include the rejection of a positive CMV status in line with the establishment's donor selection policy and Preparation Process Dossier (PPD).	**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.		
b) There are procedures for all licensable activities that ensure integrity of tissue and / or cells and minimise the risk of contamination.	Although the establishment has standard operating procedures (SOPs) covering procedures for obtaining consent, procurement and processing, there are no documented procedures relating to the storage of tissue and the release of tissue to clients for end use. In addition, the establishment has no documented procedures setting out the acceptable time frames and temperatures required to maintain antibiotic quality before discard is necessary. Further, written procedures are not sufficiently detailed to ensure consistency. For example, • the SOP for labelling has not been updated to include steps for the application of the Single European Code (SEC); • there are no documented procedures for the packing of consumables and reagents into the 'kit' used for each processing event; and • the SOP for processing has not been updated to reflect the change in storage location of the antibiotics.	**Major (cumulative)**
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.	The establishment's document control system is not restricted to authorised persons and allows all staff to modify SOPs. There is no control system that ensures only current and approved documents are in use.	
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 establishment does not record the batch numbers of settle plates and broths used for environmental monitoring of the isolator and clean room.	

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.	There is no current agreement in place between the establishment and the testing laboratory; this was due for review in 2016. The establishment uses an external third party for weighing a critical reagent used in processing. Although the partnership had recently ceased, there was no agreements in place for this activity.	
t) There are procedures for the re-provision of service in an emergency.	There are no documented procedures in place for the reprovision of services during emergencies, including, for example, re-commissioning of critical equipment or the clean room.	
GQ2 There is a documented system of quality management and audit.		
a) There is a quality management system which ensures continuous and systematic improvement.	There is no change control procedure in place for the transitioning of the establishment's older electronic management system to a newer version setting out steps to ensure there is no loss of critical data.	**Minor**
b) There is an internal audit system for all licensable activities.	An internal audit encompassing the full range of licensable activities had not been performed. There is insufficient oversight of licensable activities at the third party testing laboratory.	**Minor**
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.	The establishment has not undertaken an independent audit aimed at assessing compliance against all HTA standards.	**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 does not have adequate systems in place to ensure that their processing procedures continue to achieve their intended results. For example, the establishment has set limits for the residual water content of processed products. However, the establishment does not regularly evaluate products to ensure that these limits continue to be met. Furthermore, there is no ongoing screening of processed samples to identify potential contamination. The lack of screening is of concern as the establishment has not defined bioburden limits for amniotic membranes prior to processing; the establishment's routine post-processing sterility checks, in isolation, are insufficiently validated to ensure that potential contamination of products will be detected.	**Major**
GQ4 There is a systematic and planned approach to the management of records.		
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.	The establishment has no documented procedures which clearly set out which raw data is considered critical and should be retained for the 10 year time frame.	**Minor**
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.	At the time of the inspection, the establishment did not have contingency procedures in place to transfer records to a HTA-licensed establishment in accordance with Directions 002/2018. *The establishment have provided evidence to address this shortfall prior to issue of the final report. The HTA has assessed the information provided as satisfactory and considers this standard to be met.*	**Minor**
GQ6 A coding and records system facilitates traceability of bodies, body parts, tissues and cells, ensuring a robust audit trail.		
d) The requirements of the Single European Code are adhered to as set out in Directions 002/2018.	The Single European Code is not preceded with the letters SEC. *The establishment have provided evidence to address this shortfall prior to issue of the final report. The HTA has assessed the information provided as satisfactory and considers this standard to be met.*	**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 has not set out alert limits during environmental monitoring of processing activities that would require corrective and preventative actions taking place.	**Minor**
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.	Risk assessments have not been documented for all practices and processes.	**Minor**

Premises, Facilities and Equipment

Standard	**Inspection findings**	**Level of shortfall**
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.	There is no formal documentation capturing all risks associated with premises, facilities and equipment.	**Minor**
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.	The establishment does not currently have in place a nominated medical/scientific advisor to provide guidance on donor selection, procurement and testing activities.	**Minor**
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.	The establishment does not hold data which shows that antibiotics held at the research department were at suitable temperatures.	**Minor**

b) There are systems to deal with emergencies on a 24 hour basis.	The new freezer recently set up for antibiotic storage relies on a wireless network system supplied by a third party for call-outs to staff in the event of temperature excursions. There are no contingency arrangements in place with the third party company to ensure staff are alerted to Wi-Fi failures, procedures to test the call-out system or arrangements in place for staff to check and log temperatures during possible power outages during weekends and holidays.	**Minor**
PFE5 Equipment is appropriate for use, maintained, quality assured, validated and where appropriate monitored.		
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.	There are no procedures in place to maintain the temperature probes.	**Minor**
e) There are documented agreements with maintenance companies.	There is no documented agreements for the maintenance of the 37ºC incubator used in processing.	**Minor**

Advice

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

No.	Standard	Advice
1.	GQ2a	The DI should review the format of the processing forms to determine if all sections are necessary as the inspection team noted unused tick boxes within the form. If required, the DI should ensure all blank sections of the form are consistently completed and regularly audited to avoid discrepancies.
2.	GQ2b	The DI is advised to include observational audits of staff obtaining consent and staff carrying out processing in the establishment's internal audit schedule. The DI should also ensure a review of maintenance contractor reports is incorporated into the schedule.
3.	GQ2b	The DI is advised to put in place a process to assess donor travel history and country of donor origin in line with current epidemiological risks as reported by the European Centre of Disease Prevention and Control (ECDC) and Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC).
4.	GQ3e	Processing is currently being performed by a core team of trained staff. However, the DI is advised to put in place a re-appraisal programme setting out time frames when staff need to be re-trained and gowning re-validated. The establishment has plans to expand their services to allow higher numbers of

		amniotic membranes to be processed. The DI should ensure a robust induction and training programme is put in place prior to expansion, covering consent, processing, storage and release of tissue products. If the expansion is accompanied by a modification of its procedures, then an appropriate PPD should be submitted prior to activities commencing.
5.	GQ3k	The establishment is reliant on one member of staff for all release checks. In the staff member's absence, there is a risk that the released tissue products do not meet the required criteria.The DI should ensure a training programme is in place to ensure other staff are competent in the assessment of the final products for release.
6.	GQ7a	The DI is advised to amend the SOP for SAEARs reporting to set out the correct procedures for reporting a SAEAR to the HTA, via the HTA portal, for immediate notification.
7.	PFE2c	The DI should ensure the boxes used to transport the tissue from the maternity wards to the processing facility are cleaned appropriately between each use.
8.	PFE3a	The DI is advised to review the temperature maps of the cold room used for the storage of testing kits in the testing laboratory to ensure the kits are stored at the required temperatures. Temperature monitoring of the cold room relies on temperature probes located towards the centre of the room, while the PCR testing kits are located next to the entrance door which is frequently in use.
9.	PFE3a	The DI is advised to review the use of research grade phosphate buffered saline where there are clinical grade reagents available.
10.	PFE5b	The DI should ensure that maintenance reports by engineers who maintain the whole site are reviewed by staff responsible for the critical equipment used in activities carried out under this licence.
11.	PFE5c	The DI is advised to consider the use of swabs to supplement the environmental monitoring in hatches.
12.	PFE5d	The establishment has put in place a new medical refrigerator and freezer for the storage of tissue and critical reagents. The freezer is monitored by two different temperature systems - an 'internal' probe linked to the temperature display and an 'external' probe linked to a continuous electronic monitoring system. There are clear discrepancies between the temperatures recorded by both probes and with both probes reacting markedly differently to external stimulus. The DI is advised to ensure the freezer is temperature mapped and all probes validated prior to use.

Concluding comments

There are a number of areas of practice that require improvement, which has resulted in two major and fifteen minor shortfalls. The major shortfalls are related to the absence of documented for key activities, and the absence of systems to ensure that processing continues to achieve the intended results. The minor shorfalls are related to consent forms, change control procedures, internal and independent audits, application of the SEC, risk assessments, procedures for the retention of raw data, procedures for the transfer of records, equipment monitoring and maintenance, absence of temperature records for the antibiotic cocktail used in processing, environmental monitoring alert limits, third party agreements, absence of arrangements in an emergency and recording of all consumables and reagents.

The HTA requires that the Designated Individual addresses the shortfalls by submitting a completed corrective and preventative action (CAPA) plan within 14 days of receipt of the final report (refer to Appendix 2 for recommended timeframes within which to complete actions). The HTA will then inform the establishment of the evidence required to demonstrate that the actions agreed in the plan have been completed.

The HTA has assessed the establishment as suitable to be licensed for the activities specified subject to corrective and preventative actions being implemented to meet the shortfalls identified during the inspection.

Report sent to DI for factual accuracy: 9 July 2018

Report returned from DI: 20 July 2018

Final report issued: 13 August 2018

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: 11 November 2019

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 002/2018 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 Directions 002/2018 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 002/2018.
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 002/2018.

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 002/2018, is collected and maintained.
g) There is a system to ensure records are secure and that donor confidentiality is maintained in accordance with Directions 002/2018.
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 002/2018 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 002/2018.
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 002/2018.
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 002/2018.
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.
d) The requirements of the Single European Code are adhered to as set out in Directions 002/2018.
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 002/2018.
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 002/2018.
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.

Human Tissue Act 2004 Standards

Consent standards
C1 Consent is obtained in accordance with the requirements of the Human Tissue Act 2004 (HT Act) and as set out in the code of practice
a) Consent procedures are documented and these, along with any associated documents, comply with the HT Act and the HTA's Codes of Practice. b) Consent forms are available to those using or releasing relevant material for a scheduled purpose. c) Where applicable, there are agreements with other parties to ensure that consent is obtained in accordance with the requirements of the HT Act and the HTA's Codes of Practice. d) Written information is provided to those from whom consent is sought, which reflects the requirements of the HT Act and the HTA's Codes of Practice. e) Language translations are available when appropriate. f) Information is available in formats appropriate to the situation.
C2 Staff involved in seeking consent receive training and support in the essential requirements of taking consent
a) There is suitable training and support of staff involved in seeking consent, which addresses the requirements of the HT Act and the HTA's Codes of Practice. b) Records demonstrate up-to-date staff training. c) Competency is assessed and maintained.

Governance and quality system standards
GQ1 All aspects of the establishments work are governed by documented policies and procedures as part of the overall governance process
a) Ratified, documented and up-to-date policies and procedures are in place, covering all licensable activities. b) There is a document control system. c) There are change control mechanisms for the implementation of new operational procedures. d) Matters relating to HTA-licensed activities are discussed at regular governance meetings, involving establishment staff. e) There is a system for managing complaints.
GQ2 There is a documented system of audit
a) There is a documented schedule of audits covering licensable activities. b) Audit findings include who is responsible for follow-up actions and the timeframes for completing these.

GQ3 Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills
a) Qualifications of staff and all training are recorded, records showing attendance at training.
b) There are documented induction training programmes for new staff.
c) Training provisions include those for visiting staff.
d) Staff have appraisals and personal development plans.
GQ4 There is a systematic and planned approach to the management of records
a) There are suitable systems for the creation, review, amendment, retention and destruction of records.
b) There are provisions for back-up / recovery in the event of loss of records.
c) Systems ensure data protection, confidentiality and public disclosure (whistleblowing).
GQ5 There are systems to ensure that all adverse events are investigated promptly
a) Staff are instructed in how to use incident reporting systems.
b) Effective corrective and preventive actions are taken where necessary and improvements in practice are made.
GQ6 Risk assessments of the establishment's practices and processes are completed regularly, recorded and monitored
a) There are documented risk assessments for all practices and processes requiring compliance with the HT Act and the HTA's Codes of Practice.
b) Risk assessments are reviewed regularly.
c) Staff can access risk assessments and are made aware of risks during training.

Traceability standards
T1 A coding and records system facilitates the traceability of bodies and human tissue, ensuring a robust audit trail
a) There is an identification system which assigns a unique code to each donation and to each of the products associated with it.
b) A register of donated material, and the associated products where relevant, is maintained.
c) An audit trail is maintained, which includes details of: when and where the bodies or tissue were acquired and received; the consent obtained; all sample storage locations; the uses to which any material was put; when and where the material was transferred, and to whom.
d) A system is in place to ensure that traceability of relevant material is maintained during transport.
e) Records of transportation and delivery are kept.
f) Records of any agreements with courier or transport companies are kept.
g) Records of any agreements with recipients of relevant material are kept.

T2 Bodies and human tissue are disposed of in an appropriate manner
a) Disposal is carried out in accordance with the HTA's Codes of Practice. b) The date, reason for disposal and the method used are documented.

Premises, facilities and equipment standards
PFE1 The premises are secure and fit for purpose
a) An assessment of the premises has been carried out to ensure that they are appropriate for the purpose. b) Arrangements are in place to ensure that the premises are secure and confidentiality is maintained. c) There are documented cleaning and decontamination procedures.
PFE2 There are appropriate facilities for the storage of bodies and human tissue
a) There is sufficient storage capacity. b) Where relevant, storage arrangements ensure the dignity of the deceased. c) Storage conditions are monitored, recorded and acted on when required. d) There are documented contingency plans in place in case of failure in storage area.
PFE3 Equipment is appropriate for use, maintained, validated and where appropriate monitored
a) Equipment is subject to recommended calibration, validation, maintenance, monitoring, and records are kept. b) Users have access to instructions for equipment and are aware of how to report an equipment problem. c) Staff are provided with suitable personal protective equipment.

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 shortfall which poses a significant risk to human safety and/or dignity or is a breach of the Human Tissue Act 2004 (HT Act) or associated Directions,

Or

A 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 breach in the relevant Codes of Practices, the HT Act and other relevant professional and statutory guidelines;

or

A shortfall which indicates a failure to carry out satisfactory procedures 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.

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.