Site visit inspection report on compliance with HTA minimum standards

National Institute for Biological Standards and Control - NIBSC

HTA licensing number 22502

Licensed for the

- **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)**

29-30 May 2019

Summary of inspection findings

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

Although the HTA found that the National Institute for Biological Standards and Control – NIBSC (the establishment) had met many of the HTA's standards, five minor shortfalls were found in relation to: the absence of an internal audit schedule; the absence of validation of a specific environmental monitoring procedure; the absence of a documented procedure for the retention of records following termination of activities; an incomplete system for identifying non-conformances in environmental monitoring data and; incomplete environmental monitoring of all processing steps.

Advice has been given relating to the Governance and Quality, and Premises, Facilities and Equipment standards, as well as advice on licence management.

Particular examples of good practice are included in the concluding comments section of the report.

The HTA's regulatory requirements

The HTA must assure itself that the Designated Individual (DI), Licence Holder (LH), premises and practices are suitable.

The statutory duties of the DI 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 licenses against four groups of standards:

- consent
- governance and quality systems
- premises facilities and equipment
- disposal.

This is an exception-based report: only those standards that have been assessed as not met are included. Where the HTA determines that a standard is not met, the level of the shortfall is classified as 'Critical', 'Major' or 'Minor' (see Appendix 2: Classification of the level of shortfall). Where HTA standards are fully met, but the HTA has identified an area of practice that could be further improved, advice is given to the DI.

Reports of HTA inspections carried out from 1 November 2010 are published on the HTA's website.

Licensable activities carried out by the establishment

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

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

Tissue Category; Tissue Type	Procurement	Processing	Testing	Storage	Distribution	Import	Export
Other; hESCs		**E**	**E***	**E**	**E***		**E***

Background to the establishment and description of inspection activities undertaken

This report refers to the activities carried out by the National Institute for Biological Standards and Control (NIBSC; the establishment), which was issued an HTA licence in January 2008. This was the sixth HTA site visit inspection of the establishment (the last inspection was in May 2017) and the first since the amended Human Tissue (Quality and Safety for Human Application) Regulations 2007 came into force on 1 April 2018 [Q&S Regulations (as amended)]. The current inspection was a routine one to assess whether the establishment is continuing to meet the HTA's standards.

NIBSC is a centre of the Medicines and Healthcare products Regulatory Agency (MHRA). It has the core functions of control and evaluation of biological medicines, and development

and provision of international biological standards and references. The UK Stem Cell Bank (UKSCB) was established in 2003 and forms part of the NIBSC Advanced Therapies Division (ATD).

NIBSC is licensed under the Q&S Regulations (as amended) for the processing, testing, storage, distribution and export of tissues and cells for human application.

The DI is a Principal Scientist in ATD and the LH is the Director of NIBSC. There are two Persons Designated (PDs) working under the licence: the UKSCB Production and Deputy Production Managers.

The role of the UKSCB is to provide a repository of human embryonic stem cell (hESC) lines, to be used as starting material for developing Advanced Therapy (Investigational) Medicinal Products [AT(I)MPs]. The deposited hESC lines were derived from embryos obtained under the donor selection and informed consent requirements as defined by the Human Fertilisation and Embryology (HFE) Act (1990) (as amended) and overseen by the Human Fertilisation and Embryology Authority (HFEA). The derivation and culturing of the initial hESC lines was undertaken by other HTA-licensed establishments (the 'Derivation Laboratories').

UKSCB's activities are overseen by an independent national 'Steering Committee' (the 'Steering Committee for the UKSCB and the use of Stem Cell Lines') working to a Code of Practice. Following Steering Committee approval, the hESC line is deposited after a due diligence process against the European Union Tissues and Cells Directives (EUCTDs) has been performed. These are 'EUTCD-grade' cell lines. Upon receipt from the Derivation Laboratory, the hESC lines are quarantined as a seed stock. This is used to provide cells for quality control (QC) and cell characterisation, as well as stocks for the creation of a 'Pre-Master Cell Bank'. Cell line characterisation, growth and handling requirements are recorded in each Cell Line Master File (CLMF).

Each hESC line is allocated a unique identifier (UKSCB accession number) and a Single European Code Donation Identification Sequence (SEC-DI). The accession number and SEC-DI are included on the vial label and in any accompanying documentation.

Processing

The Master Cell Bank is derived by expanding the Pre-Master Cell Bank in a processing facility. This bank forms the seed stock for the derivation of a Distribution Cell Bank. The Distribution Cell Banks are the hESC lines that are available for developing AT(I)MPs.

The processing facility comprises a clean room containing four aseptic laboratories. Each laboratory contains two laminar air flow cabinets capable of maintaining a grade A processing environment in a background of grade B. Temperature-sensitive reagents and consumables used during processing are stored in monitored and alarmed refrigerators and freezers.

All critical systems, including air handling units and incubators, and the status of the clean room (pressures and particle counts) are continuously monitored and alarmed. The monitoring is controlled by a specialised system linked to the NIBSC Environmental Monitoring System (EMS), which alerts establishment staff to any system failures.

At the time of the inspection, the processing facility was undergoing maintenance and the clean room was not in operation.

Storage

The processed cells are cryopreserved for a minimum of 24 hours by passive freezing in a -80°C freezer. They are then transferred to a -150°C mechanical (quarantine) freezer. Following review of QC and environmental monitoring data by the UKSCB Production

Manager, vials are moved to vapour phase storage in the 'release' liquid nitrogen storage vessel (cryovessel). Cryovessels and freezers are linked to the NIBSC EMS, which feeds into a wired callout system. Temperature excursions outside the set ranges trigger both audible alarms and the callout system and the system is tested regularly.

Maintenance staff perform monthly checks of the temperature charts and alert the DI to any discrepancies (see *Advice*, item 6).

The facility has fixed oxygen-depletion monitors linked to the alarm system, as well as portable monitors. The cryovessels are filled automatically every two days and contingency cryovessels are available. Cryovessels and freezers are subject to regular service and probes are calibrated annually under contract.

UKSCB has classified 38 EUTCD-grade hESC lines. To date, four of these are available for use in AT(I)MP development, 20 are pending the completion of due diligence or QC and 14 are pending banking.

UKSCB also provides a repository for human adult, foetal and embryonic stem cell lines and induced pluripotent stem cell lines for research; these are 'Laboratory-grade' cell lines.

The timetable for the site visit inspection was developed after consideration of the establishment's previous inspection report, communications with the HTA since the last inspection and annual activity data. The inspection included a visual inspection of the processing facility and cryostore, and the area used for sample receipt and release. Roundtable discussions were held with relevant staff to review processing and storage records, and to discuss the management of audits, incidents and risk assessments. Interviews were held with the DI and the LH.

Audits of traceability were carried out:

- Two vials of separate EUTCD-grade cell lines were selected at random from the -150°C freezer and storage locations, and labelling details, were compared to the paper and electronic records. There were no discrepancies noted.
- The electronic records and CLMFs of three separate EUTCD-grade cell lines were reviewed. As well as a review of processing, QC, labelling, cryopreservation and storage data, the training records of the relevant processing staff were also reviewed. There was one discrepancy noted in the environmental monitoring data [see shortfall against standard GQ7(a)].

Inspection findings

The HTA found the DI and the LH to be suitable in accordance with the requirements of the legislation.

Compliance with HTA standards

Governance and Quality

Standard	Inspection findings	Level of shortfall
GQ2 There is a documented system of quality management and audit.		
b) There is an internal audit system for all licensable activities.	The only audits carried out are by the NIBSC Quality Department and these are considered to be independent audits to meet standard GQ2(c). There is no schedule of internal audits.	**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's procedures allow for environmental monitoring plates used during processing to be stored at 2-8°C for up to 48 hours prior to incubation. The establishment was unable to provide a validation of this process.	**Minor**
GQ4 There is a systematic and planned approach to the management of records.		
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.	There is an agreement with an HTA-licensed establishment for the transfer of cells in the event of licence termination. The establishment plans to extend this agreement to cover the storage of traceability records and raw data, but this has not yet been completed.	**Minor**
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.	The establishment does not have a robust procedure in place for identifying and responding to adverse events linked to the non-viable particle monitoring equipment used during processing. Currently, the establishment accepts an absence of alerts as evidence that no excursions have occurred during processing. However, in December 2018, cells were processed during a period when the monitoring system was not working; the absence of alerts during this period was not informative and the fact that the monitoring system was not working was not identified.	**Minor**

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 002/2018.	As part of processing, NIBSC carries out full environmental monitoring for some steps (thawing of seed stocks, final preparation of master and distribution cell banks) but not the intermediate sub-culturing steps leading to the formation of master and distribution cell banks.	**Minor**

Advice

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

No.	Standard	Advice
1.	N/A	The establishment will be responsible for the transport of 'released' hESC lines to organisations involved in the manufacture of AT(I)MPs. This constitutes 'release for circulation' (not release for end use) and is not 'Distribution' as defined by the Q&S Regulations (as amended). The DI is advised to consider removing the activity of 'Distribution' from the licence held under the Q&S Regulations (as amended).
2.	GQ3(f)	The establishment has a detailed HTA training guide which provides the context of the activities at the UKSCB and how this relates to the legislative requirements. However, some staff have not been trained using this guide since 2016. The DI is advised to ensure that all staff are fully up to date with this training.
3.	GQ3(f)	The DI is advised to consider incorporating the Q&S Regulations Test Questions, created by the HTA, into the establishment's regulatory training programme.
4.	GQ6(d)	The SEC requirements vary depending upon the time when tissues and cells have been procured and stored. The establishment has been storing hESC lines received from Derivation Centres since 2010. The DI is advised to refer to the 'HTA guidance on coding and import regulations for tissues and cells in the human application sector' (page 9) for the different SEC requirements for each time period (before 29 October 2016, 29 October 2016-1 April 2018, after 1 April 2018).
5.	GQ8(c)	Although staff can access risk assessments, the DI is advised to consider introducing a system whereby staff 'sign-off' that they have read and are familiar with risk assessments, similar to the process used for standard operating procedures.
6.	PFE2(b), 3(c)	The DI is advised to document the procedure that describes the frequency, types of checks and staff responsible for the review of raw data, including temperature charts and environmental monitoring data.

Concluding comments

During the inspection, an area of good practice was noted:

- Staff carrying out the independent audits have the option of being trained to audit to ISO9001: 2015 standards by an external organisation.

There are a number of areas of practice that require improvement, including five minor shortfalls. The HTA has given advice to the DI with respect to the Governance and Quality, and Premises, Facilities and Equipment standards, as well as advice on licence management.

The HTA requires that the DI 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: 16 July 2019

Report returned from DI: 24 July 2019

Final report issued: 13 August 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

Governance and Quality

Standard
GQ1 All aspects of the establishment's work are supported by ratified documented policies and procedures as part of the overall governance process.
a) There is an organisational chart clearly defining the lines of accountability and reporting relationships.
b) There are procedures for all licensable activities that ensure integrity of tissue and / or cells and minimise the risk of contamination.
c) There are regular governance meetings, for example health and safety, risk management and clinical governance committees, which are recorded by agendas and minutes.
d) There is a document control system to ensure that changes to documents are reviewed, approved, dated and documented by an authorised person and only current documents are in use.
g) There are procedures to ensure that an authorised person verifies that tissues and / or cells received by the establishment meet required specifications.
h) There are procedures for the management and quarantine of non-conforming consignments or those with incomplete test results, to ensure no risk of cross contamination.
i) There are procedures to ensure tissues and / or cells are not released from quarantine until verification has been completed and recorded.
j) There are procedures detailing the critical materials and reagents used and where applicable, materials and reagents meet the standards laid down by the European directives on medical devices and in vitro diagnostic medical devices.
k) There is a procedure for handling returned products.
l) There are procedures to ensure that in the event of termination of activities for whatever reason, stored tissues and / or cells are transferred to another licensed establishment or establishments.
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.

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.
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.
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.
h) Users have access to instructions for equipment and receive training in the use of equipment and maintenance where appropriate.

i) Staff are aware of how to report an equipment problem.
j) For each critical process, the materials, equipment and personnel are identified and documented.
k) There are contingency plans for equipment failure.

Disposal

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

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

Where the HTA determines that a licensing standard is not met, the improvements required will be stated and the level of the shortfall will be classified as 'Critical', 'Major' or 'Minor'. Where the HTA is not presented with evidence that an establishment meets the requirements of an expected standard, it works on the premise that a lack of evidence indicates a shortfall.

The action an establishment will be required to make following the identification of a shortfall is based on the HTA's assessment of risk of harm and/or a breach of the Human Tissue Act 2004, Human Tissue (Quality and Safety for Human Application) Regulations 2007 or the HTA Directions.

1. **Critical shortfall:**

   A shortfall which poses a significant risk to causing harm to a recipient patient or to a living donor,

   or

   A number of 'major' shortfalls, none of which is critical on its own, but viewed cumulatively represents a systemic failure and therefore is 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 straight away.

2. **Major shortfall:**

   A non-critical shortfall.

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

   or

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

   or

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

   or

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

   or

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

   In response to a major shortfall, an establishment is expected to implement corrective and preventative actions within 1-2 months of the issue of the final inspection report. Major shortfalls pose a higher level of risk and therefore a shorter deadline is given, compared to

minor shortfalls, to ensure the level of risk is reduced in an appropriate timeframe.

3. **Minor shortfall:**

   A shortfall which cannot be classified as either critical or major and which can be addressed by further development by the establishment.

   This category of shortfall requires the development of a corrective action plan, the results of which will usually be assessed by the HTA either by desk-based review or at the time of the next inspection.

   In response to a minor shortfall, an establishment is expected to implement corrective and preventative actions within 3-4 months of the issue of the final inspection report.

Follow up actions

A template corrective and preventative action plan will be sent as a separate Word document with both the draft and final inspection report. You must complete this template and return it to the HTA within 14 days of the issue of the final report.

Based on the level of the shortfall, the HTA will consider the most suitable type of follow-up of the completion of the corrective and preventative action plan. This may include a combination of

- a follow-up site visit inspection
- a request for information that shows completion of actions
- monitoring of the action plan completion
- follow up at next desk-based or site-visit inspection.

After an assessment of the proposed action plan the establishment will be notified of the follow-up approach the HTA will take.