

NuVision Biotherapies Ltd
HTA licensing number 22656

Licensed under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended)
and
Licensed under the Human Tissue Act 2004

Licensable activities carried out by the establishment

Licensed activities

'E' = Establishment is licensed to carry out this activity and is currently carrying it out.

'TPA' = Third party agreement; the establishment is licensed for this activity but another establishment (not licensed by the HTA) carries out the activity on their behalf.

Site	Procurement	Processing	Testing	Storage	Distribution	Import	Export
NuVision Biotherapies Ltd	E/TPA	E	E/TPA	E	E		E

Licensed activities – Human Tissue Act 2004

'Licensed' = Establishment is licensed to carry out this activity and is currently carrying it out.

Area	Storage of relevant material which has come from a human body for use for a scheduled purpose
NuVision Biotherapies Ltd	Licensed

Tissue types authorised for licensed activities

Authorised = Establishment is authorised to carry out this activity and is currently carrying it out.

Tissue Category; Tissue Type	Procurement	Processing	Testing	Storage	Distribution	Import	Export
Membrane, Amniotic; Amniotic Membrane	Authorised	Authorised	Authorised	Authorised	Authorised		Authorised

Summary of VRA findings

The HTA found the Designated Individual (DI) and the Licence Holder (LH) 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's standards that were assessed during the virtual regulatory assessment (VRA), three minor shortfalls were found against standards for Governance and Quality. These shortfalls relate to the limited scope of the independent audit, absence of temperature monitoring data for the maternal blood samples and risk assessments not being reviewed annually. Following the VRA and prior to the issuing of the draft report, the establishment provided evidence to satisfy the HTA that the two shortfalls relating to independent audits and temperature monitoring data have been addressed.

The HTA has assessed the establishment as suitable to be licensed for the activities specified.

Compliance with HTA standards

Minor Shortfalls

Standard	VRA findings	Level of shortfall
GQ2 There is a documented system of quality management and audit.		
c) An audit is conducted in an independent manner at least every two years to verify compliance with protocols and HTA standards, and any findings and corrective actions are documented.	<p>The independent audit provided a high level of assurance of compliance with HTA standards by confirming the appropriate standard operating procedures (SOPs) were in place. However, there was no evidence that primary records had been reviewed to verify that the SOPs were being followed.</p> <p><i>During the VRA, the establishment submitted sufficient evidence to address this shortfall before the report was finalised.</i></p>	Minor

GQ4 There is a documented system of quality management and audit.

<p>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</p>	<p>On the day of procurement, the maternal blood is often taken ahead of the planned caesarean. To maintain the safety of the blood samples and the procuring kit, these are stored in a fridge near the theatre. The temperature of this fridge has not been monitored.</p> <p><i>During the VRA, the establishment submitted sufficient evidence to address this shortfall before the report was finalised.</i></p>	<p>Minor</p>
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GQ8 Risk assessments of the establishment's practices and processes are completed regularly and are recorded and monitored appropriately.

<p>b) Risk assessments are reviewed regularly as a minimum annually or when changes are made that may affect the quality and safety of tissues and cells.</p>	<p>The establishment has a comprehensive list of risk assessments but not all the risk assessments have been reviewed in line with regulatory requirements.</p>	<p>Minor</p>
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Advice

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

Number	Standard	Advice
1.	C1(b)	Potential donors are identified in advance of their planned caesarean. However, it is only on the day of surgery that the consent form and the medical questionnaire is completed. The DI is advised to consider approaching potential donors in advance and at a time when they are less likely to be distracted by the impending procedure.
2.	GQ1(b)	As a result of an incident in October 2019, the SOP S-PO5 had to be amended. Although all staff have been made aware of the changes, to date this SOP has not been finalised. In line with the establishment's procedures to close off corrective actions for incidents within six months, the DI is advised to finalise and issue this SOP.
3.	GQ4(k)	New end users are informed by the establishment of the requirement to hold a valid HTA licence if they intend to store Omnigen for more than 48 hours. To avoid any confusion, the DI is advised to change the wording to "licensed by the HTA under the Human Tissue (Quality and Safety for Human Application) Regulations 2007" as establishments licensed only under the Human Tissue Act (2004) are not permitted to store tissue for human application.
4.	PFE2(b)	The DI is advised to consider implementing a procedure to undertake periodic monitoring for contamination within the establishment's processing facility of hard to reach areas, such as the corners of the isolator hatches which cannot be reached using contact plates, or the isolator sleeves which should not be exposed to a contact plate.
5.	PFE2(b)	The DI is advised to consider identifying any positive sterility results detected during environmental monitoring and to monitor for trends.

6.	PFE5(b)	The DI is advised to have a system to test the temperature alarm system to ensure it works as expected.
7.	PFE5(c)	Part of the processing procedure requires incubation of the tissue within a tight temperature range. Before use, the temperature of the incubator is verified by noting the in-built digital temperature display. The DI is advised to implement a procedure for regularly confirming that the displayed temperature corresponds to the actual temperature within the incubator.

Background

The establishment specialises in the production of a vacuum-dried, amnion-derived product called Omnigen, which can be stored at temperatures between 2°C to 25°C for up to 60 weeks. The amniotic membrane used for the manufacture of Omnigen is procured from donors undergoing elective caesarean sections at a nearby hospital. The 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 procured, the amniotic membrane is double-bagged in sterile saline and transported in labelled boxes back to the establishment for processing.

The establishment is also licensed for the storage of relevant material for use in a Scheduled Purpose. This activity was not reviewed as part of the VRA.

NuVision Biotherapies Ltd has been licensed by the HTA since November 2015. This was the establishment's first VRA undertaken by the HTA. The most recent previous inspection took place in June 2018.

Since the site inspection in June 2018, a satellite site was added but this has since been revoked by the establishment.

Description of VRA activities undertaken

The HTA's regulatory requirements are set out in Appendix 2. The following areas were covered during the VRA:

Records relating to donor consent, procurement, processing, storage and release for end-use were reviewed for one Omnigen product in conjunction with establishment staff. As part of the discussion, equipment maintenance records, consumable and reagent storage temperature records, staff training and equipment/operator validation were also reviewed. The consent form for a second amniotic membrane was examined to confirm consent for use in research had been given.

Details of four incidents were reviewed, as well as the corrective actions taken as a result of a Serious Adverse Event (SAE).

The COVID - 19 pandemic has had a significant impact on the timely delivery of products. Discussions were held about the steps the establishment takes to ensure that their product is not stored on unlicensed premises for more than the permitted 48 hours.

Three audits related to testing, processing, and equipment and consumables were reviewed.

Report sent to DI for factual accuracy: 3 December 2020

Report returned from DI: 9 December 2020

Final Report issued: 11 December 2020

Appendix 1: HTA standards

The HTA standards applicable to this establishment are shown below; those not assessed during the VRA 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
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 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.
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.
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.
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: The HTA's regulatory requirements

The HTA must assure itself that the DI, Licence Holder, 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 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 3: 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 and Virtual Regulatory Assessments carried out from 1 November 2010 are published on the HTA's website.

Appendix 3: 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 associated Directions.

1. Critical shortfall:

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

or

A number of 'major' shortfalls, none of which is critical on its own, but viewed cumulatively represent a systemic failure and therefore are considered 'critical'.

A critical shortfall may result in one or more of the following:

- A notice of proposal being issued to revoke the licence
- 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.
- A notice of suspension of licensable activities
- Additional conditions being proposed
- Directions being issued requiring specific action to be taken straightaway

2. Major shortfall:

A non-critical shortfall.

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

or

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

or

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

or

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

or

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

In response to a major shortfall, an establishment is expected to implement corrective and preventative actions within 1-2 months of the issue of the final VRA 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 on-site inspection or VRA.

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 VRA.

Follow up actions

A template corrective and preventative action plan will be sent as a separate Word document with the final VRA. Establishments 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 routine site-visit inspection.

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