Licence application assessment visit report on compliance with HTA licensing standards
Site visit date: **24 May 2023**

Megagen Implants UK Ltd

Proposed HTA licensing number 22697

Application for a licence under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended)

Licensable activities applied to be carried out by the establishment

Proposed licensed activities

'E' = Establishment applied to be licensed to carry out this activity and will carry it out.

Site	Procurement	Processing	Testing	Storage	Distribution	Import	Export
Megagen Implants UK Ltd				E	E	E	E

Tissue types applied to be authorised for licensed activities

Applied to be authorised = Establishment to be authorised to carry out this activity and will currently be carrying it out.

Tissue Category; Tissue Type	Procurement	Processing	Testing	Storage	Distribution	Import	Export
Musculoskeletal, Bone; Acellular Bone				Applied to be authorised	Applied to be authorised	Applied to be authorised	Applied to be authorised

Musculoskeletal, Bone; Cancellous Bone Particles				Applied to be authorised	Applied to be authorised	Applied to be authorised	Applied to be authorised

Summary of visit findings

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

Although the HTA found that Megagen Implants UK Ltd (the proposed establishment) had met the majority of the HTA's standards, one major and ten minor shortfalls were found against standards for Governance and Quality, and Premises, Facilities and Equipment.

The HTA has assessed the proposed 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 visit.

Compliance with HTA standards

Major Shortfalls

Standard	Visit 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.		
n) The establishment ensures imports from third countries meet the standards of quality and safety set out in Directions 001/2021.	The proposed importing tissue establishment (ITE) intends to import acellular bone products from a third country supplier (3CS) in the EU. The supplier identifies potential donors using a medical selection questionnaire. The questionnaire does not collect information about whether potential donors have had any recent exposure to live attenuated viruses. *The proposed establishment submitted sufficient evidence to address this shortfall before the report was finalised.*	**Major**

Minor Shortfalls

Standard	Visit 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.		
n) The establishment ensures imports from third countries meet the standards of quality and safety set out in Directions 001/2021.	The draft agreement between the proposed ITE and the 3CS does not contain, as a minimum, the requirements set out in Directions 001/2021. Specifically, paragraph 255g of the HTA Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment (The Guide), is not present. In addition, the proposed ITE did not have a summary of the most recent inspection of the 3CS by the third country competent authority.	**Minor**

GQ2 There is a documented system of quality management and audit.		
b) There is an internal audit system for all licensable activities.	At the time of the assessment, there was no proposed approach for the internal audit system for all proposed licensable activities.	**Minor**

GQ4 There is a systematic and planned approach to the management 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.	At the time of the assessment, there was no proposed system for the regular audit of records and their content to check for completeness, legibility and accuracy and to resolve any discrepancies found.	**Minor**
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 documented retention times for raw data which are critical to the safety and quality of tissues and cells are not aligned to regulatory requirements.	**Minor**
i) The minimum data to ensure traceability from donor to recipient as required by Directions 001/2021 are kept for 30 years after the use, expiry or disposal of tissues and / or cells.	The documented retention times for traceability data are not aligned to regulatory requirements.	**Minor**
m) In the event of termination of activities of the establishment a contingency plan is in place to ensure raw data and records of traceability are maintained for 10 or 30 years respectively, as required.	Although the proposed establishment has a contingency plan, it does not include arrangements for transferring records to a HTA licensed establishment in accordance with Directions 001/2021.	**Minor**

GQ7 There are systems to ensure that all adverse events 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 documented procedure for incident management does not include the requirement that the initial notification to the HTA should be given within 24 hours of the discovery or determination of the serious adverse event (SAE) or serious adverse reaction (SAR) by the proposed establishment. In addition, the timeframe within which end-users must report SAEs or SARs to the proposed establishment is not specified.	**Minor**
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.	There is no system for receiving and distributing national and local information to end-users.	**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.	The proposed establishment has not carried out risk assessments for all practices and processes related to proposed licensable activities. For example, the process for receiving deliveries and actively managing the transport of products to end-users.	**Minor**

PFE4 Systems are in place to protect the quality and integrity of bodies, body parts, tissues and cells during transport and delivery to a destination.		
i) Primary packaging containing tissues and / or cells is labelled with the information required by Directions 001/2021.	At the time of the assessment, there was no system in place to meet the requirement set out in paragraph 167c of The Guide.	**Minor**

Advice

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

Number	Standard	Advice
1.	GQ1d	The proposed DI is advised to document which personnel are responsible for document review and approval, and describe the system used to ensure only current documents are in use.
2.	GQ1h	Once the product storage arrangements are confirmed, and before commencing licensable activities, the proposed DI should document the procedures for the management and quarantine of non-conforming products.
3.	GQ1k	At the time of the assessment, the proposed DI advised that the proposed licensed establishment would not accept returned products from end-users. Before commencement of activity, this position should be clarified and the documented procedure updated as required.
4.	GQ1n	The draft agreement between the proposed licensed establishment and the 3CS provides assurance that products comply with country specific regulatory requirements. The proposed DI is advised to include the

		documented procedure for product review and release, within the quality management system (QMS) of the proposed licensed establishment.
5.	GQ3e GQ3f	The proposed DI should ensure all applicable training is completed by staff carrying out tasks related to licensable activities before the activities are started. In addition, the proposed DI should ensure the training programme includes sufficient information to ensure staff have adequate knowledge of the scientific and ethical principles relevant to their work, and the regulatory context.
6.	GQ4a	The proposed DI is advised to describe in more detail the processes for the creation, identification, maintenance, access, amendment, retention and destruction of records, in the documented procedure.
7.	GQ4k	The proposed DI should ensure the documented agreements with end-users include the requirements set out in paragraphs 153 and 154 of The Guide.
8.	GQ7f	The proposed DI is advised to review and update the recall procedure to include notification to the HTA, and the pre-defined times in which actions must be taken.
9.	PFE4b	Before commencing licensable activities, the proposed DI should update the documented procedures for transport, including the packaging instructions once they are confirmed.
10.	PFE3c PFE4e PFE4g	The proposed establishment provided information about how they are assured that short term temperature deviations from the specified storage temperature range are acceptable and do not impact the quality and safety of the products. The DI is advised to document this information within the QMS.

11.	D1c D2a	Before commencing licensable activities and in the event products are returned to the proposed licensed establishment for disposal, the proposed DI should document the disposal procedure, including tracking the disposal of products that details the method and reason for disposal. .

Background

The proposed establishment has applied to be licensed for import, storage, distribution, and export of acellular bone and cancellous bone particles. There is a draft agreement in place between the proposed establishment and the 3CS located in Germany.

Description of activities undertaken during visit

The HTA's regulatory requirements are set out in Appendix 1. The Regulation Manager covered the following areas during the visit:

Standards assessed against during visit

Standards covered at this assessment are listed in Appendix 3. Any standards that were not applicable to the proposed establishment have been deleted from this table. Any standards that were applicable, but were not covered during the assessment, have been highlighted in grey.

Review of governance documentation

The assessment included a review of policies and procedural documentation relevant to the establishment's proposed licensable activities. This included procedures describing receipt and storage, labelling, packaging and distribution, recall, and incident management. The assessment also included a review of the draft agreement with the 3CS and associated documents including those describing donor selection and consent, donor testing, batch record review and product release, and labelling.

Visual inspection

The assessment consisted of a visual inspection of the main reception area, to which products will be delivered, and the room which will be used as the area for product storage, packaging, and distribution.

Meetings with staff
The assessment included discussions with the Managing Director, who is the proposed Corporate Licence Holder Contact (CLHc), and the Operations Director, who is the proposed DI.

Report sent to proposed DI for factual accuracy: 23 July 2024

Report returned from proposed DI: No factual accuracy or request for redaction comments were made

Final report issued: 16 August 2024

Appendix 1: 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 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.

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 (as amended), 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, or;
   - 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 (as amended) 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 the final inspection report. 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, or;
- 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.

Appendix 3: 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 (as amended)

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.

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 third countries meet the standards of quality and safety set out in Directions 001/2021.
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 001/2021.
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.

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 001/2021.
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 001/2021 are kept for 30 years after the use, expiry or disposal of tissues and / or cells.
k) There are documented agreements with end users to ensure they record and store the data required by Directions 001/2021.
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 001/2021 (Northern Ireland only).
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.

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.
c) There are procedures for cleaning and decontamination.

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 001/2021.
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 001/2021.
j) Shipping packaging containing tissues and / or cells is labelled with the information required by Directions 001/2021.
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.