

Gilead Sciences Ltd
Proposed HTA licensing number 22683

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.

'E*' = Establishment applied to be licensed to carry out this activity but will not carry it out.

'TPA' = Third party agreement; the establishment applied to be licensed for this activity but another establishment (not licensed by the HTA) will carry out the activity on their behalf.

Site	Procurement	Processing	Testing	Storage	Distribution	Import	Export
Hub Gilead Sciences Ltd							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.

Applied to be authorised* = Establishment to be authorised to carry out this activity but will not currently be carrying it out.

Tissue Category; Tissue Type	Procurement	Processing	Testing	Storage	Distribution	Import	Export
Mature Cell, MNC; PBMC							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.

Gilead Sciences Ltd (GSL; 'the establishment') was found to have met all HTA standards.

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

Compliance with HTA standards

All applicable HTA standards have been assessed as fully met.

Advice

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

Number	Standard	Advice
1.	GQ2b and GQ4b	The establishment has proposed a governance framework where establishment staff, and the proposed DI, oversee licensable activity undertaken by a partner organisation. The roles and responsibilities for each party are clearly documented in agreements, however the proposed DI is advised to undertake regular audits to ensure that they maintain oversight of day-to-day activities, that procedures are followed as expected, and that any incidents related to the licensable activity are escalated to the proposed DI as appropriate.
2.	GQ4m	With reference to paragraphs 267-270 of the HTA's Guide to Quality and Safety Assurance for Tissues and Cells for Patient Treatment, the proposed DI is advised to consider updating establishment documentation to include actions to be taken in the event the licence is terminated.

3.	PFE4a	The procurement and testing of PBMCs will occur under the authority of another HTA licence. However, exported tissue must comply with the requirements set out in the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended). The proposed DI is advised to update establishment documentation to clearly indicate this requirement.
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Background

GSL has applied to be licensed for the export of peripheral blood mononuclear cells (PBMCs) for use as starting material for Advanced Therapy Medicinal Products (ATMPs). GSL has agreements with hospitals in the UK that will procure and test PBMCs under an existing HTA licence, in line with the requirements of the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended). GSL and each UK hospital also have an agreement with a partner facility in Europe. The European partner facility will qualify each hospital as being suitable to procure the ATMP starting material, and will subsequently arrange for the physical shipment of each exported cell sample. Each export will be arranged using a proprietary software system and coordinated through a Case Manager at GSL, with appropriate oversight from the proposed DI. GSL has agreements in place to undertake regular process and document audits of each hospital, and the European partner facility.

Description of activities undertaken during visit

The HTA's regulatory requirements are set out in Appendix 1. Due to the national response to the COVID-19 pandemic, no site visit was undertaken. The Regulation Manager covered the following areas during a remote (desk-based) assessment.

Standards assessed against during visit

Standards covered at this assessment are listed in Appendix 3. Any standards that were not applicable to the 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 activity of Export, and the traceability and quality management systems (QMS). This included procedures describing the process for notifying the European partner facility to arrange for export and for the DI to provide oversight of the activity. Third party agreements were reviewed, as was documentation around the validation of the procurement site, the export process, and the traceability and incident reporting systems.

Visual inspection

There was no on-site assessment undertaken and therefore no visual inspection.

Meetings with establishment staff

A desk-based assessment was undertaken which included discussions with the proposed DI, the proposed Corporate Licence Holder contact (CLHc) the proposed primary Persons Designated for the licence, and with the Senior Director for Quality Assurance responsible for the activities at the European partner facility.

Report sent to proposed DI for factual accuracy: 01 April 2021

Report returned from proposed DI: 19 April 2021

Final report issued: 05 May 2021

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

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

Consent
C2 Information about the consent process is provided and in a variety of formats.
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.
Governance and Quality
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.
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.
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.

k) There are documented agreements with end users to ensure they record and store the data required by Directions 002/2018.
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.
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

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.

- 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.
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.
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.