Site visit inspection report on compliance with HTA licensing standards

ADC Therapeutics (UK) Ltd

HTA licensing number 12664

Licensed under the Human Tissue Act 2004 for the

- **storage of relevant material which has come from a human body for use for a scheduled purpose**

19 February 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 ADC Therapeutics (UK) Ltd (the establishment) had met the majority of the HTA's standards, six minor shortfalls were found. The shortfalls were in relation to: (i) document consistency and control; (ii) internal audit; (iii) recording and acting on adverse events; (iv) a documented procedure for disposal; (v) a documented procedure for cleaning and decontamination and; (vi) a documented contingency plan.

Advice has been given relating to the Governance and quality system, and Premises, facilities and equipment standards, as well as advice on licence management.

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

The HTA's regulatory requirements

Prior to the grant of a licence, the HTA must assure itself that the Designated Individual (DI) is a suitable person to supervise the activity authorised by the licence and that the premises are suitable for the activity.

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.

Its programme of site visit inspections to assess compliance with HTA licensing standards is one of the assurance mechanisms used by the HTA.

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. They are grouped under four headings:

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

This is an exception-based report: only those standards that have been assessed as not met are included. Where the HTA determines that there has been a shortfall against a standard, 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 provided.

HTA inspection reports are published on the HTA's website.

Background to the establishment

This report refers to the activities carried out by ADC Therapeutics (UK) Ltd ('the establishment'). The establishment was issued an HTA licence in February 2017 and this was the first site visit inspection under the licence. The current inspection was a routine site visit to assess whether the establishment is continuing to meet the HTA's standards.

ADC Therapeutics was founded in 2012 and is based in Switzerland, with operations in the UK (Research & Development, R&D) and the USA (Clinical Development and Chemistry, Manufacturing and Controls, CMC). The company's work focuses on the development of proprietary pyrrolobenzodiazepine dimer antibody drug conjugates (PBD-ADCs) for the treatment of both solid and haematological malignancies. The UK operation is based at the Queen Mary BioEnterprises Innovation Centre in Whitechapel, London.

The establishment is licensed under the Human Tissue Act 2004 for the storage of relevant material for use for a scheduled purpose. Relevant material from living donors is currently being stored for the scheduled purpose of 'research in connection with disorders, or the functioning, of the human body' ('research').

The DI supervising activities taking place under the licence is a Principal BioAnalytical Scientist within the company, the Corporate Licence Holder (CLH) is ADC Therapeutics (UK) Ltd and the CLH Contact (CLHC) is the R&D Senior Vice President. There are currently no Persons Designated (PDs) working under the licence (see *Advice*, item 1).

The establishment currently purchases material from a HTA-licensed commercial supplier under a 'Terms and Conditions' agreement associated with each purchase. The agreement ensures that appropriate and valid consent has been sought from donors and that samples are transported appropriately. All agreements are set up following completion of a detailed 'due diligence questionnaire' which is sent by ADC Therapeutics to all its suppliers.

The establishment is currently storing 10 bone marrow mononuclear cell (BMMC) samples under the licence.

Tracking and labelling system

Samples are received into the establishment in validated temperature-monitored dry shippers or dry ice containers. There are integrity checks of the sample and the temperature of the shipment packaging as well as checks of the paperwork. There is no specific procedure for managing non-conformances [see shortfall against standard GQ5(a)].

Sample details provided by the supplier (name, catalogue number, batch number) are entered into the electronic tracking system which generates a unique identification number. Sample locations are also recorded on the tracking system, along with sample removal, use and disposal.

Storage

Samples are stored in secure areas in lockable, isothermal liquid nitrogen storage vessels (cryovessels) and -80°C freezers. Cryovessel and freezer space is available as a contingency.

The cryovessels and freezers are linked to a continuous temperature-monitoring unit, which feeds into an automated, wireless callout system. Temperature excursions outside the set ranges trigger both local audible alarms and the callout system but the system is not tested regularly (see *Advice*, item 9). There are no labels indicating steps to be taken if the audible alarms sound (see *Advice*, item 10).

There are oxygen depletion monitors in the liquid nitrogen storage facility linked to an alarm system. The isothermal jacket of each cryovessel is occasionally topped up with liquid nitrogen.

The storage facilities are under maintenance contracts and there are regular service visits.

Disposal

Samples are disposed of but there are different documents covering the disposal of human samples [see shortfall against standard GQ1(a)].

Description of inspection activities undertaken

The timetable for the site visit inspection was developed after consideration of the establishment's licence application, compliance update information and communications with the HTA. The inspection included a visual inspection of the site (sample receipt and storage areas), discussions and interviews with key staff, and a review of documentation. Interviews were held with the DI and CLHC.

Traceability audits were performed on eight stored samples. The samples were randomly selected from each storage facility (four from a -80°C freezer, four from a cryovessel) and labelling and location details were compared to the electronic records. There were no discrepancies noted.

Inspection findings

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

Compliance with HTA standards

Governance and Quality

Standard	Inspection findings	Level of shortfall
GQ1 All aspects of the establishments work are governed by documented policies and procedures as part of the overall governance process		
a) Ratified, documented and up-to-date policies and procedures are in place, covering all licensable activities. b) There is a document control system. c) There are change control mechanisms for the implementation of new operational procedures.	ADC Therapeutics has a set of global policies and procedures (e.g. Global Code of Conduct; Global Data Protection Policy; ADCT-SOP-90 General Laboratory Safety) which are under rigorous document control. However, the documents created locally by the establishment are a mixture of: • Uncontrolled procedures (e.g. (i) Protocol: Receipt and tracking of samples and materials; (ii) Freezerworks audit). • Risk assessments and procedures in a single document (e.g. (i) ADCTRA-001: Whole blood and PBMC risk assessment; (ii) ADCTRA-003: Use and disposal of various human materials and tissues risk assessment) • Uncontrolled work instructions (e.g. (i) Guide to Freezerworks-Adding materials; (ii) Guide to Freezerworks-Tracking and removing materials). There is currently no consistency in the creation, standardisation, review and control of these documents.	**Minor**
GQ2 There is a documented system of audit		
a) There is a documented schedule of audits covering licensable activities.	An internal audit system encompassing the full range of licensed activities has not been implemented. The establishment performs regular checks to ensure that the inventory of human samples matches records on the electronic database. However, this does not constitute an internal audit aimed at assessing compliance against the full range of applicable standards under the HT Act. See *Advice*, item 4.	**Minor**

GQ5 There are systems to ensure that all adverse events are investigated promptly		
a) Staff are instructed in how to use incident reporting systems.	There is no system or documented procedure for recording adverse events relating to human samples or for recording the actions to be taken as a result of the adverse event occurring. See *Advice*, item 7.	**Minor**

Traceability

T2 Bodies and human tissue are disposed of in an appropriate manner		
b) The date, reason for disposal and the method used are documented.	The procedure for disposal of human tissue is covered by a wide range of controlled and uncontrolled documents (e.g. (i) ADCT-SOP-090 General Laboratory Safety; (ii) ADCTRA-001: Whole blood and PBMC risk assessment; (iii) ADCTRA-003: Use and disposal of various human materials and tissues risk assessment, (iv) Protocol: Receipt and tracking of samples and materials; (v) Guide to Freezerworks-Tracking and removing materials). There is currently no consistency in the documentation which requires the recording of date and reason for disposal, and the method used.	**Minor**

Premises, Facilities and Equipment

Standard	**Inspection findings**	**Level of shortfall**
PFE1 The premises are secure and fit for purpose		
c) There are documented cleaning and decontamination procedures.	There are no documented cleaning and decontamination procedures.	**Minor**
PFE2 There are appropriate facilities for the storage of bodies and human tissue		
d) There are documented contingency plans in place in case of failure in storage area.	There are informal contingency plans in place in case of a storage facility failure but there are no documented plans.	**Minor**

Advice

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

No.	Standard	Advice
1.	N/A	The DI is advised to consider appointing a PD to assist her in the role. This would be especially important on those occasions when the DI is absent. The HTA must be notified of such an appointment.
2.	C1(d)	As reinforced in more detail in the HTA's Code of Practice on Research, imported material should be procured, used, handled, stored, transported and disposed of in accordance with the consent which has been obtained. As part of their assurance with the supplier that appropriate and valid consent has been taken, the establishment has obtained templates of the participant information sheet and consent form used in material sourced in the USA. The DI is advised to consider confirming with the supplier that: (i) Consent has been given for tissue to be exported from the USA; (ii) Consent is not limited in terms of duration of sample storage.
3.	GQ1(d)	The establishment currently has regular meetings of the Compliance Senior Working Group and ADC Therapeutics R&D Group to discuss governance issues. The DI is advised to consider adding an HTA standing agenda item to one of these meetings. This should facilitate the standardisation of documents, changes to standard operating procedures (SOPs), audits and their findings, competence and training, management of adverse events, risk assessments, equipment maintenance and discussion of updates from the HTA (e.g. e-newsletter items).
4.	GQ2(a)	Although this is not exhaustive, the DI is advised to include in the audit schedule: (i) audits of documentation (e.g. procedures, forms) to ensure accuracy and consistency and; (ii) procedural audits of the establishment's activities to help assure the DI that current practices adequately reflect the content of SOPs. The results of all audit findings, and actions taken, should be formally recorded and discussed at suitable meetings, to ensure continuing improvement of processes and practices.
5.	GQ3(a)	The DI is advised to consider recording the attendance of staff at the HTA training presentation given by the Quality Manager.
6.	GQ3(a),	The DI is advised to consider the following resources for use in the staff training programme: • The MRC 'Research and Human Tissue Legislation e-learning Module'. • The HRA e-learning module 'Research involving human tissue'. • The HTA 'Code of Practice and Standards on Research (Code E)'.
7.	GQ5(a), (b)	The HTA's 'Code E: Research Standards and guidance' document provides further information on adverse event reporting: 'All establishments licensed by the HTA are required to have an internal system for reporting adverse events and, where necessary, instigating an investigation or root cause analysis. Clearly assigning responsibilities for incident management is important. As the DI is responsible for licensed activities at the establishment, there should be a

		process in place to allow them to be made aware of adverse events so that proper investigation and reporting can take place. There should be an adverse incident SOP detailing how adverse incidents are logged, reported, addressed and monitored. Although there is currently no requirement for establishments in the research sector to report adverse incidents to the HTA, if a DI has concerns about an adverse event, they are encouraged to contact us for further advice. Relevant examples of adverse events include: • specimen loss; • missing or incorrect documentation; • security breach; • abnormalities in storage temperature readings; • inappropriate disposal'.
8.	PFE2(c)	The DI is advised to ensure that the set temperature ranges for the alarm system are documented and are recorded on labels on cryovessels and freezers.
9.	PFE2(c)	The DI is advised to consider regular testing of the temperature alarm callout system to ensure that it is functioning correctly.
10.	PFE2(c)	The DI is advised to consider placing labels on cryovessels and freezers to summarise procedures to take when the audible temperature alarms are activated.
11.	PFE2(c)	The DI is advised to consider initiating a programme by which, at suitable timeframes, the temperature plots from the monitoring system are reviewed. This may help to identify a potential failure of the system before it occurs.

Concluding comments

During the inspection, an area of strength was noted, in that the company consists of a small team who appear to work well together.

There are a number of areas of practice that require improvement, including six 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 the DI to submit a completed corrective and preventative action (CAPA) plan setting out how the shortfalls will be addressed, 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: 19 March 2019

Report returned from DI: 1 April 2019

Final report issued: 25 April 2019

Completion of corrective and preventative actions (CAPA) plan

Based on information provided, the HTA is satisfied that the establishment has completed the agreed actions in the CAPA plan and in doing so has taken sufficient action to correct all shortfalls addressed in the Inspection Report.

Date: 23 June 2022

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.

Consent standards
C1 Consent is obtained in accordance with the requirements of the Human Tissue Act 2004 (HT Act) and as set out in the code of practice
c) Where applicable, there are agreements with other parties to ensure that consent is obtained in accordance with the requirements of the HT Act and the HTA's Codes of Practice.

Governance and quality system standards
GQ1 All aspects of the establishments work are governed by documented policies and procedures as part of the overall governance process
a) Ratified, documented and up-to-date policies and procedures are in place, covering all licensable activities. b) There is a document control system. c) There are change control mechanisms for the implementation of new operational procedures. d) Matters relating to HTA-licensed activities are discussed at regular governance meetings, involving establishment staff. e) There is a system for managing complaints.
GQ2 There is a documented system of audit
a) There is a documented schedule of audits covering licensable activities. b) Audit findings include who is responsible for follow-up actions and the timeframes for completing these.
GQ3 Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills
a) Qualifications of staff and all training are recorded, records showing attendance at training. b) There are documented induction training programmes for new staff. c) Training provisions include those for visiting staff. d) Staff have appraisals and personal development plans.
GQ4 There is a systematic and planned approach to the management of records
a) There are suitable systems for the creation, review, amendment, retention and destruction of records. b) There are provisions for back-up / recovery in the event of loss of records. c) Systems ensure data protection, confidentiality and public disclosure (whistleblowing).

GQ5 There are systems to ensure that all adverse events are investigated promptly
a) Staff are instructed in how to use incident reporting systems.
b) Effective corrective and preventive actions are taken where necessary and improvements in practice are made.
GQ6 Risk assessments of the establishment's practices and processes are completed regularly, recorded and monitored
a) There are documented risk assessments for all practices and processes requiring compliance with the HT Act and the HTA's Codes of Practice.
b) Risk assessments are reviewed regularly.
c) Staff can access risk assessments and are made aware of risks during training.

Traceability standards
T1 A coding and records system facilitates the traceability of bodies and human tissue, ensuring a robust audit trail
a) There is an identification system which assigns a unique code to each donation and to each of the products associated with it.
b) A register of donated material, and the associated products where relevant, is maintained.
c) An audit trail is maintained, which includes details of: when and where the bodies or tissue were acquired and received; the consent obtained; all sample storage locations; the uses to which any material was put; when and where the material was transferred, and to whom.
d) A system is in place to ensure that traceability of relevant material is maintained during transport.
e) Records of transportation and delivery are kept.
f) Records of any agreements with courier or transport companies are kept.
g) Records of any agreements with recipients of relevant material are kept.
T2 Bodies and human tissue are disposed of in an appropriate manner
a) Disposal is carried out in accordance with the HTA's Codes of Practice.
b) The date, reason for disposal and the method used are documented.

Premises, facilities and equipment standards
PFE1 The premises are secure and fit for purpose
a) An assessment of the premises has been carried out to ensure that they are appropriate for the purpose.
b) Arrangements are in place to ensure that the premises are secure and confidentiality is maintained.
c) There are documented cleaning and decontamination procedures.

PFE2 There are appropriate facilities for the storage of bodies and human tissue
a) There is sufficient storage capacity. c) Storage conditions are monitored, recorded and acted on when required. d) There are documented contingency plans in place in case of failure in storage area.
PFE3 Equipment is appropriate for use, maintained, validated and where appropriate monitored
a) Equipment is subject to recommended calibration, validation, maintenance, monitoring, and records are kept. b) Users have access to instructions for equipment and are aware of how to report an equipment problem. c) Staff are provided with suitable personal protective equipment.

Appendix 2: Classification of the level of shortfall

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

The action an establishment will be required to make following the identification of a shortfall is based on the HTA's assessment of risk of harm and/or a breach of the HT Act or associated Directions.

1. **Critical shortfall:**

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

   or

   A combination of several major shortfalls, none of which is critical on its own, but which together could constitute a critical shortfall and should be explained and reported as such.

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

   (1) A notice of proposal being issued to revoke the licence

   (2) Some or all of the licensable activity at the establishment ceasing with immediate effect until a corrective action plan is developed, agreed by the HTA and implemented.

   (3) A notice of suspension of licensable activities

   (4) Additional conditions being proposed

   (5) Directions being issued requiring specific action to be taken straightaway

2. **Major shortfall:**

   A non-critical shortfall that:

   - poses a risk to human safety and/or dignity, or
   - indicates a failure to carry out satisfactory procedures, or
   - indicates a breach of the relevant CoPs, the HT Act and other relevant professional and statutory guidelines, or
   - has the potential to become a critical shortfall unless addressed

   or

   A combination of several minor shortfalls, none of which is major on its own, but which, together, could constitute a major shortfall and should be explained and reported as such.

   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, but which indicates a departure from expected standards.

   This category of shortfall requires the development of a corrective action plan, the results of either which will usually be assessed by the HTA by desk based or site visit inspection.

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

Follow up actions

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

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

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

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