Site visit inspection report on compliance with HTA minimum standards

Roslin Cells Limited

HTA licensing number 22631

Licensed for the

- **procurement, processing, testing, storage, distribution and import/export of human tissues and cells for human application under the Human Tissue (Quality and Safety for Human Application) Regulations 2007**

27 January 2015

Summary of inspection findings

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

Although the HTA found that Roslin Cells Limited (the establishment) had met the majority of the HTA standards, a minor shortfall was found in that the establishment had no contingency plan for transfer of traceability records and raw data in the event it ceases to remain licensed by the HTA.

Since the last HTA inspection, no further procurement of tissues or cells has taken place, so the activity carried out under the HTA licence has been limited to on-going storage of cells for use as starting material for cell lines. Other activity has been carried out under a licence from the Medicines and Healthcare products Regulatory Agency (MHRA). Accordingly, many of the HTA standards do not apply and advice has been provided to the DI regarding the extent of the HTA licence required for current activity.

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

The HTA's regulatory requirements

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

The statutory duties of the Designated Individual 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.

Licensable activities carried out by the establishment

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

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

'TPA' = Third party agreement; the establishment is licensed for this activity but another establishment (unlicensed) carries out the activity on their behalf.

Tissue type	Procurement	Processing	Testing	Storage	Distribution	Import	Export
Embryonic stem cells	**E***	**E***	**E***	**E**	**E***	**E***	**E***

Background to the establishment and description of inspection activities undertaken

This report refers to the activities carried out by Roslin Cells Ltd (the establishment). The establishment is licensed for the procurement, testing, processing, storage, distribution and import/export of human tissues and cells under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 and has been licensed by the HTA since March 2008. It has previously undertaken procurement activities under a research licence issued by the

Human Fertilisation and Embryology Authority (HFEA), but this is in the process of being revoked as such activity is no longer being carried out.

The establishment is also licensed by the Medicines and Healthcare products Regulatory Agency (MHRA) for manufacturing both Investigational Medicinal Products and 'Specials'. In advance of this inspection, the HTA liaised with the MHRA inspector who carried out the most recent MHRA Good Manufacturing Practice (GMP) inspection, to ascertain if any findings were relevant to this inspection. The inspector confirmed that only minor issues had been raised and had subsequently been addressed by the establishment.

This report describes the establishment's third routine site visit inspection.

The establishment is a not-for-profit company set up with the aim to derive undifferentiated, clinical grade, human embryonic stem cell lines for research and therapeutic application. In addition to supplying clinical and research grade pluripotent stem cells, the company now provides contract manufacturing and cell therapy development services to commercial and academic partners. The company is now located within the Scottish Centre for Regenerative Medicine (SCRM), a purpose-built translational facility owned by the University of Edinburgh and part funded by Scottish Enterprise. The building comprises research laboratories used by the University of Edinburgh and a GMP translational facility, which is shared by the establishment and the Scottish National Blood Transfusion Service (SNBTS), each having their own clean rooms and supporting laboratories and offices. The establishment worked together with SNBTS to set up a combined, overarching, quality management system, with separate local policies and procedures where appropriate. The close working relationship is also evidenced by both establishments being involved in joint governance meetings and the sharing of the results of trending of environmental monitoring.

The establishment carries out processing within two Grade B clean rooms, each containing two microbiological safety cabinets capable of providing a Grade A environment, supported by a Grade C cleanroom, support rooms for administration and consumable storage, and tissue culture and analytical laboratories.

Environmental monitoring of the cleanrooms is conducted regularly 'at rest' and is also performed throughout cell processing using a combination of the facility's in-built environmental monitoring system and settle/contact/finger dab plates. Air sampling is both passive and active.

Culture and analysis of media plates is carried out either by the establishment or at nearby laboratories run by SNBTS. Trending of results is carried out and the establishment has robust procedures governing action to be taken should alert or action limits be approached.

Cell storage within the establishment is in vapour phase of liquid nitrogen within two secure, monitored and alarmed vessels.

At the time of this inspection, the establishment had not procured tissues for the derivation of new stem cell lines since the last inspection. Consequently, related activities, such as donor assessment/testing, were not being undertaken either directly by the establishment or under appropriate agreements with third parties. In the past, the establishment has had agreements in place with a number of HFEA-licensed Assisted Conception Units (ACUs) for such work and previous procurement was carried out under that licence. However, any future procurement is likely to involve tissues and cells which fall within the remit of the HTA under this licence.

Other than continuing storage, no other HTA licensable activity was being carried out at the time of the inspection. The establishment has been carrying out testing for infectious diseases, mandatory serology testing having previously been carried out at time of procurement. This testing is carried out under the terms of a service level agreement with a specialist laboratory. As this testing is in addition to the original donor assessment/testing that

was carried out at the ACUs under the auspices of their HFEA licences, it does not fall within the remit of the HTA licence but has been used in connection with quality assurance of processing.

The establishment does not import tissues or cells at present and carries out no distribution of tissues or cells under the HTA licence. Any release of cells as cell lines falls under the remit of the MHRA.

The inspection comprised a visual inspection of the facility, including areas for tissue/cell receipt and storage and the areas used for processing, document review and round table discussions of the quality system and environmental monitoring with key staff, as well as an interview with the DI. The HTA did not enter the cleanrooms, as these were recently inspected under the MHRA licence and no issues of concern to the HTA were raised.

An audit of traceability in storage was performed. The lead HTA inspector chose not to request the removal of any cells from the vapour phase storage, in case there was a risk of thermal shock damage. Local log book records of the storage locations for a group of vials held in four storage box locations were cross-checked with appropriate records held within the relevant files and associated batch records.

The batch records for one cell line actively being worked on and one which was in storage ready for release were reviewed to ensure that they contained all relevant documentation, including consent forms, serology and microbiology test results, and the results of environmental monitoring. No discrepancies were noted.

Inspection findings

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

Compliance with HTA standards

Governance and Quality

Standard	Inspection findings	Level of shortfall
GQ4 There is a systematic and planned approach to the management of records.		
m) In the event of termination of activities of the establishment a contingency plan to ensure records of traceability are maintained for 10 or 30 years as required.	The establishment has no documented contingency plan to deal with the requirement that traceability records and raw data continue to be held on HTA licensed premises in the event the establishment ceases to be licensed by the HTA. The continued storage of such records, accessible by the HTA, is required to aid traceability and investigation in the event of notification of a serious adverse event or reaction related to tissues or cells which have been procured, processed or stored by the establishment. Advice has also been provided under this standard, below. **This shortfall was addressed by the establishment in advance of publication of the final inspection report.**	**Minor**

Advice

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

No.	Standard	Advice
1.	C1, C2, C3	The HTA notes that previous procurements were carried out under the establishment's HFEA licence and that the consent documentation, procedures and the consenting process, were under the auspices of that licence. Although licensed for the activity, no procurement under the HTA licence has taken place. However, the HTA also notes that in future the establishment may wish to procure tissues and cells under its HTA licence if requested to do so as part of contract work for clients and advises the DI to ensure that appropriate policies, procedures and documentation are put in place, together with the required training of staff. If appropriate to the circumstances, Third Party Agreements should be put in place with suitably qualified and trained procurement staff. The HTA also advises the DI to consider, as an alternative, whether the establishment requires to be licensed for procurement if such procurement could be carried out by agreement with another HTA licensed establishment.
2.	GQ4m	The DI is advised to explore whether a suitable records storage contingency plan could be agreed with SNBTS, given the close working relationship between the two organisations.

3.	PFE3c	The DI is advised to formalise an alarm challenge procedure and the results of challenges, to ensure that alarm function is recorded. The current procedure, whereby alarms are triggered informally during activities such as accessing storage locations, presents a risk that staff fail to notice alarm malfunction.
4.	N/A	The HTA notes that the establishment is licensed for all activities carried out under an HTA licence for Human Application. The HTA also notes that the only licensable activities which have been, and are currently being carried out, are processing and storage. Consent and procurement have previously been carried out under the establishment's HFEA licence and, as cells are processed into master cell lines, as such fall within the remit of the MHRA. No distribution or import has been carried out under the HTA licence and there are no plans to do so in the near future. Should export be carried out, it will be of non HTA licensed materials. It is likely that processing will be carried out, under the HTA licence, in the future. The DI is advised to consider the activities for which the establishment is licensed in the light of current activity and future plans for development, and to notify the HTA if the current licensable activities should be changed.

Concluding comments

The HTA saw various examples of good practice during the inspection. Establishment staff have worked very closely with SNBTS to create an overarching quality system governing aspects of the infrastructure and procedures shared by both establishments, and have created local procedural and policy documentation using a similar format, ensuring consistency.

Restriction of access to cleanrooms by trained staff only is reinforced by the use of laminated lists of entitled staff on the doors leading to each facility, acting as a visual reminder.

Access to the various laboratories within the cleanroom suite is also restricted to appropriately qualified and trained staff and the use of different colour coded laboratory coats helps ensure that only appropriate staff access restricted areas of the establishment.

Trending of environmental monitoring results has been shared in a reciprocal arrangement with SNBTS and this has had benefits in identifying areas for improvement.

The sign off procedures at each stage of processing appear to be very robust, with multiple steps being crosschecked and signed at various intermediate tissue "release" steps and a final release procedure involving staff from production and quality areas of the establishment.

There is an area of practice that requires to be improved, resulting in one minor shortfall. The HTA has given advice to the DI with respect to documentation and staff training in the event procurement is to be carried out under this licence, alarm challenge procedures and the activities for which the establishment requires to be licensed.

The HTA requires that the DI addresses the shortfall by submitting a completed corrective and preventative action (CAPA) plan within 14 days of receipt of the final report (refer to Appendix 2 for recommended timeframes within which to complete actions). The HTA will

then inform the establishment of the evidence required to demonstrate that the actions agreed in the plan have been completed.

The HTA has assessed the establishment as suitable to be licensed for the activities specified subject to corrective and preventative actions being implemented to meet the shortfall identified during the inspection.

Report sent to DI for factual accuracy: 9 February 2015

Report returned from DI: 23 February 2015

Final report issued: 23 February 2015

Inspection CAPA Plan Closure Statement:

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 February 2015

Appendix 1: HTA standards

The HTA standards applicable to this establishment are shown below; those not assessed during the inspection are shown in grey text. Individual standards which are not applicable to this establishment have been excluded.

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

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.
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.

Governance and Quality

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

p) There are written agreements with third parties whenever an activity takes place that has the potential to influence the quality and safety of human tissues and / or cells.
q) There is a record of agreements established with third parties.
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 003/2010, is collected and maintained.
g) There is a system to ensure records are secure and that donor confidentiality is maintained in accordance with Directions 003/2010.
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 003/2010 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.
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.
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.
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 003/2010.
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.
PFE5 Equipment is appropriate for use, maintained, quality assured, validated and where appropriate monitored.
a) Critical equipment and technical devices are identified, validated, regularly inspected and records are maintained.
b) Critical equipment is maintained and serviced in accordance with the manufacturer's instructions.
c) Equipment affecting critical processes and storage parameters is identified and monitored to detect malfunctions and defects and procedures are in place to take any corrective actions.
d) New and repaired equipment is validated before use and this is documented.
e) There are documented agreements with maintenance companies.
f) Cleaning, disinfection and sanitation of critical equipment is performed regularly and this is recorded.
h) Users have access to instructions for equipment and receive training in the use of equipment and maintenance where appropriate.
i) Staff are aware of how to report an equipment problem.
j) For each critical process, the materials, equipment and personnel are identified and documented.
k) There are contingency plans for equipment failure.

Disposal

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

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

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

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

(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.

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

or

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

or

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

or

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

or

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

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

3. **Minor shortfall:**

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

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

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

Follow up actions

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

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

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

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