ATMP development and the role of the HTA
A brief history of the HTA

- The Human Tissue Act 2004 enshrines consent for the use of tissue and organs in law
- It was created following events at hospitals, where tissue had been removed and stored without consent
- The HTA was founded in 2005, to ensure that the removal, storage and use of tissue and organs is undertaken safely, ethically and with proper consent
Sectors regulated and associated legislation

Human Tissue Act (HT Act)
- Post mortem
- Anatomy
- Research
- Public display

Licensing & inspection

Living donation
- Assessment of living donation
  Living organ donation and bone marrow, & peripheral blood stem cells from people who lack the capacity to consent

EU Tissues & Cells Directives
- Human Application
- Licensing & inspection

EU Organ Donation Directives
- Organ donation and transplant
- Licensing & inspection
European Union Tissues and Cells Directives (EUTCD)

- Set out to produce a harmonised approach to the regulation of tissues and cells for patient treatment across Europe
- Directives set a benchmark for standards that must be met when carrying out activities involving tissues and cells for patient treatment
- Focus on Quality and Safety
- Require that systems are in place to ensure all tissues and cells (and any derived products) are traceable from donor to recipient
Human Tissue (Quality and Safety for Human Application) Regulations 2007

- The HTA is the Competent Authority in the UK for the EUTCD for tissues and cells, other than gametes and embryos
  
  \textit{(HFEA - Competent Authority for gametes & embryos)}

- EUTCD was transposed into UK Law 2007

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

- Human Application licences are required under the Quality and Safety Regulations when establishments carry out certain activities
Procurement → Testing (donor virology) → Processing → Storage → Distribution → Vigilance! - SAE & SAR reporting, traceability
The HTA’s regulatory remit for ATMPs


Where an advanced therapy medicinal product contains human cells or tissues, Directive 2004/23/EC should apply only as far as donation, procurement and testing are concerned, since the further aspects are covered by this Regulation.

Eudralex Volume 4, Annex 2 - Manufacture of Biological active substances and Medicinal Products for Human Use

There may be some instances where processing of cells and tissues used as starting materials for biological medicinal products will be conducted at tissue establishments, e.g. to derive early cell lines or banks prior to establishing a Master Cell Bank (MCB). Such processing steps, are under the scope of Directive 2004/23/EC, which provides for the need of a Responsible Person (RP).
Model regulatory pathway for an ATMP derived from hESC

- **HFEA**: Human Fertilisation and Embryology Act
- **HTA**: EU Tissues and Cells Directive
- **MHRA**: EU Clinical Trials Directive
- **Embryo** → **Cellular material** → **ATMP**
- **Processing** → **Manufacture**
- **HRA (GTAC)**: UK Clinical Trials Regulations
The HTA regulatory landscape for ATMPs

**ATMP Manufacturer**
- Receives starting material from elsewhere
- Produces ATMPs
- Not HTA licensed

**ATMP Manufacturer**
- Procures starting material
- Produces ATMPs
- Procurement and testing

**Multi-Activity Establishment**
- Procures material
- Produces tissue and cell products
- Produces ATMPs
- HTA licence for all activities

**NHS Hospital**
- Procures starting material
- Distributes to ATMP manufacturer
- Procurement and testing

**Private Tissue Bank**
- Banks material on behalf of clients for potential future use
- Could be used to develop ATMP
- Procurement, testing, processing, storage
## New EU Directives for tissues & cells

Come into force in the UK in April 2017

### Import Directive - 2015/566/EC


### Coding Directive - 2015/565/EC

A single European identifying code shall be allocated to all donated material at the tissue establishment, to ensure proper identification of the donor and the traceability of all donated material and to provide information on the main characteristics and properties of tissues and cells.
How do these apply to ATMPs?

**Import Directive - 2015/566/EC**
Will apply to donation, procurement and testing of imported tissues and cells used in ATMP manufacture
Where manufacturers of ATMPs are party to a contractual agreement with a third country supplier for the import tissues and cells, they should be considered an importing tissue establishment

**Coding Directive - 2015/565/EC**
Tissues and cells used for advanced therapy medicinal products shall be traceable under this Directive at least until transferred to the ATMP manufacturer
Elements of the single European code will apply
The HTA and the Regulation of ATMPs
Donation of tissues & cells used in ATMPs

Consent considerations where donations may be used to develop products by commercial manufacturers

- That any donation is a gift and is given freely without expectation of financial benefit
- That a product could potentially be developed for widespread use
- The need for lasting traceability from donor to recipient
- Where known, the types of tests that will be carried out on a cell line and any implications

https://www.hta.gov.uk/codes-practice
Licensing considerations

Q1. When does material fall under the Q&S Regulations?
When it is a tissue or cell being collected as a starting material for the manufacture of an ATMP

Q2. What HTA licence is needed?
If material is being obtained for the purposes of ATMP manufacture, as a minimum the donation, procurement and testing will need to occur under an HTA Human Application licence

Q3. What if the primary purpose of obtaining the material is not ATMP manufacture (e.g. material taken for diagnostic biopsy or surgery for tumor removal)?
If material removed is also to be used for ATMP manufacture it will be subject to the Q&S Regulations. Some aspects of procurement may not be subject to licensing requirements – **HTA will assess on a case-by-case basis**

Q4. What if material has already been collected?
Risk assessment and gap analysis by a Designated Individual to evaluate compliance with the Q&S regulations
Licensing considerations

Q5. My product has been classified as an ATMP and I am licensed by the HTA only for procurement and testing – do I still report SAEARs to the HTA?

If the suspected SAE or SAR is linked to donor selection, procurement or donor testing then you should notify the HTA.

Agreements between procurement and manufacturing sites should detail the requirement that if a suspected SAE or SAR is discovered at any point, the licensed tissue establishment is notified without delay. The licensed tissue establishment should then report this event or reaction to the HTA.
Legislative borders for cell based therapies

Collection of starting materials - blood based starting materials regulated by HTA (EUTCD) or MHRA (EUBD)
Interim joint position published in 2015

Movement of products intended for use in ATMP manufacture
Single regulatory agency has oversight of transit of tissue and cell product from tissue establishment to ATMP manufacturer

Regulatory remit based on type of product
Potential for same cell type to have different regulatory pathway depending on intended use/extent of processing

Tissue & cell (HTA) → ATMP (MHRA)
Why do we need cross-regulator collaboration?

- Possible consequences of over-regulation*
  - Acts as a deterrent - hospitals, universities, research community
  - Potential to reduce availability of access

- Ensuring consistent regulatory advice
  - Agreed and established positions
  - Process for addressing new queries from developers

- Seamless regulatory pathway
  - Enabling transition between regulators
  - Provide a single point of entry into the regulatory system for new developers

Meeting the challenges

• Joined up inspection strategy for jointly regulated establishments
  – Tailored approach depending on activity type

• Advice – by email or in person
  – Agency specific – enquiries@hta.gov.uk
  – Regulatory Advice Service for Regenerative Medicine (RASRM) – Joint advice from multiple regulatory agencies – via the MHRA Innovation Office

• Cell Therapy History File
  – Non legislative tool
  – Support developers

• Joint policies and positions
  – Published on the HTA website
Thank you for your attention

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An independent statutory regulator sponsored by the Department of Health