Advanced Therapy Medicinal Products (ATMPs)

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Overview

• Definitions and Examples
• Regulatory Developments
• Trial Complexity
• Specific Challenges
• Product and Safety Issues
What are ATMPs?

An ATMP is a **biological** medicinal product that can be classified as either:

- Gene Therapy Medicinal Product
- Cell Therapy Medicinal Product
- Tissue Engineered Medicinal Product
- Genetically Modified Cells
- Combined ATMP + Medical Devices

[EC Regulation No 1934/2007]
Regulation (EC) No 1394/2007
Applied from 30 December 2008

of 13 November 2007
on advanced therapy medicinal products and amending Directive 2001/83/EC
and Regulation (EC) No 726/2004
(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission,

Having regard to the Opinion of the European Economic and

been defined in Annex I to Directive 2001/83/EC, but a legal definition of tissue engineered products remains to be laid down. When products are based on viable cells or tissues, the pharmacological, immunological or metabolic action should be considered as the principal mode of action. It should also be clarified that products which do not meet the definition of a medicinal product, such as products made exclusively of non-viable materials which act primarily by physical means, cannot by definition be advanced therapy medicinal products.
Commission Directive 2009/120/EC
Implemented September 2009

DIRECTIVES

COMMISSION DIRECTIVE 2009/120/EC
of 14 September 2009
code relating to medicinal products for human use as regards advanced therapy medicinal products
(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Community code relating to medicinal products for human use (1), and in particular Article 120 thereof.

(4) The measures provided for in this Directive are in accordance with the opinion of the Standing
Committee for Medicinal Products for Human Use,

HAS ADOPTED THIS DIRECTIVE:

Article 1
Part IV of Annex I to Directive 2001/83/EC is replaced by the
text set out in the Annex to this Directive.
Gene Therapy Medicinal Products (GTMP)

GTMP means a biological medicinal product which has the following characteristics:

• It contains an active substance which contains or consists of a recombinant nucleic acid used in, or administered to human beings, with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;

• Its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Gene therapy medicinal products shall NOT include vaccines against infectious disease

[Directive 2001/83/EC annex 1, Part IV; amended by 2009/120/EC]
Gene Therapy Vectors

Viral Vector Carrying Transgene → Transduction

DNA encoding Transgene

Transcription & Translation

Therapeutic Protein
Examples of GTMPs

- **genetically modified viruses**  
  e.g. adenovirus  retrovirus  lentivirus  pox virus (vaccinia)  
  herpes simplex virus

- **genetically modified cells**  
  (Cancer specific T cells)

- **oncolytic viruses**  
  (cancer treatments)

- **plasmid DNA**

- **antisense techniques**  
  (e.g. gene silencing, gene correction or gene modification)
Somatic Cell Therapy Medicinal Products (CTMP)

Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics:

a) contains or consists of cells or tissues that have been subject to **substantial manipulation** so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are **not intended to be used for the same essential function(s)** in the recipient and the donor;

b) is presented as having properties for, or is used in or administered to human beings, with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

[Directive 2001/83/EC annex 1, Part IV; amended by 2009/120/EC]
Examples of CTMPs

- **Adult Cells** autologous or allogenic cells
  - adult stem cells (multipotent)
    (ChondroCelect, cartilage repair)
  - differentiated cells
    (dendritic cells, cancer immunotherapy)

- **Embryonic stem cells** (pluripotent)
  (blindness, spinal injury)

- **Induced pluripotent stem cells** (iPS Cells)
- **Xenogenic Cells**
Tissue Engineered Medicinal Products (TEPs)

Tissue Engineerered Product (TEP)

Tissue engineered product means a product that:

- contains or consists of **engineered cells or tissues**, and
- is presented as having properties for, or is used in or administered to human beings with a view to **regenerating, repairing or replacing** a human tissue.

A TEP may contain:

- cells or tissues of **human or animal** origin, or both
- the cells or tissues may be **viable or non-viable**
- additional substances i.e. **scaffolds or matrices**
Examples of TEPs

• **In vitro Cultured Skin**
  - repair for burns or chronic wounds

• **Neo-organs** (corneal, blood vessel, liver, cartilage or bone tissue)

• **Tissue Engineered Trachea**
Regulatory Developments

1st gene modified cells into human 1989
GTAC formed 1993
First Gene Trial UK 1993
GMO contained use regulations 2000
EU Clinical Trials Directive 2001
GMO deliberate release regulations 2002
EU Tissues and Cells Directive 2004
‘Clinical Trial’ Regulations’ May 2004
SACGM Guidance, HSE 2006
HT (Q&S for Human Application) Regs 2007
EU ATMP Regulations 1394/2007 2008
EC guidance on GCP for ATMPs Dec 2009
EMEA Guideline on Follow-up of patients administered with GTMP 2010
GMP Annex 2 Revision 2010
Medicines for Human Use (ATMP and Misc amendments) Regulations’ SI 2010/1882
Bridging the Regulatory Gap

- Lack of a harmonised and tailored regulatory environment
- Divergent national approaches to legal classification and authorisation
- Uneven patient access to treatments
EU ATMP Regulations 1394/2007

- Tissue engineered products defined as medicinal products for the 1st time
- New **definitions** of gene and cell therapy products
- New ATMP specific **GMP guidelines**
- EMA Centralised procedure for Marketing Authorisation (CAT)
- 30 Year **Traceability** requirements
- Unlicensed ATMPs can be manufactured under **hospital exemption**
### Summary of some of the main differences in scope between the hospital exemption and “specials” schemes

<table>
<thead>
<tr>
<th>Hospital exemption</th>
<th>The “specials” scheme</th>
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<tbody>
<tr>
<td>The ATMP must be prepared and used in the same EU Member State</td>
<td>Products meeting the requirements of the scheme can be manufactured in the UK or imported to the UK</td>
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<tr>
<td>The ATMP must be commissioned by a medical practitioner</td>
<td>Products can be prescribed by doctors, dentists and supplementary prescribers</td>
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<tr>
<td>The ATMP must be custom made to meet an individual prescription and preparation must be on a “non-routine basis”</td>
<td>There is a special needs test (interpreted to mean the absence of a pharmaceutically equivalent and available licensed product)</td>
</tr>
<tr>
<td>The ATMP must be used in a hospital</td>
<td>There is no stipulation as to location</td>
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Multiple Regulators = Multiple requirements

- HTA Human Application License (donation, procurement, testing)
- 30 Year Traceability
- Safety Reporting HTA
- Autologous / Allogenic Donor Cells (HSC, MSC)
- Viral Vector Manufacture (AAV, Lentivirus)
- GMP MA(IMP) Manufacturing
- 30 Year Traceability
- HSE
- Genetically Modified Cells
- GMP MA(IMP) Manufacturing
- 30 Year Traceability
- HSE
- Storage Pharmacy or other controlled storage facility
- IMP Accountability GCP
- 30 Year Traceability
- HSE
- Safety Reporting HTA
- Safety Reporting MHRA
- Administration to Patient
- IMP Accountability GCP
- HSE
- 30 Year Traceability
- Patient Follow-up
- Safety Reporting MHRA
General Challenges of Advanced Therapies

• Evolving regulatory requirement
  
  Statutory Instruments 2010 No. 1882 on Medicines:
  The Medicines for Human Use (ATMPs and Miscellaneous Amendments) Regulations 2010

• Product classification

• Non-clinical models for safety, toxicology, proof of concept, clinical target dose

• Specialized facilities - GMP

• Manufacturing expertise and costs
Logistical Challenges – IMP management

WT1 TCR IMP Management Plan Flow Chart

WT1 TCR Vector manufactured by EUFETs AG Germany
Quality Control and QP Release by EUFETs

WT1 TCR Vector shipped to UCL Medical School, Royal Free Hospital

Receipt and storage of WT1 TCR Vector
Royal Free Hospital

Receipt and storage of WT1 TCR Vector
Variant

Transport of WT1 TCR Vector to individual patient treatment at GOSH OTU

Receipt & storage of WT1 TCR Vector at GOSH

Transduction of T cells with WT1 TCR Vector

Transport of WT1 TCR-transduced T Cells to storage facility

Cryopreservation WT1 TCR-transduced T Cells at GOSH/RFH/Thermofisher

Cells not QP released / expiry date exceeded

QP Release of WT1 TCR-transduced T Cells

Conditioning arranged and booked at local study hospital

Day 0 AM WT1 TCR-transduced T Cells transported to local trial centre

Day 8 - Day 4 patient conditioning

WT1 TCR-transduced T Cells receipt and check

Day 0 patient admitted (inpatient or outpatient)

Thawing of patient of WT1 TCR-transduced T Cells

Re-infusion of patient WT1 TCR-transduced T Cells
Logistical Challenges - Traceability

A system allowing complete traceability

- sourcing
- donation
- manufacturing
- packaging
- storage
- transport
- delivery & receipt
- thawing & infusion
- follow-up

- 2-tiered system for anonymity
- similar system used for blood
- long term data storage and long term planning
Product Issues: Cell Therapy / TEP

- Very short shelf life (<2 days)
- Real time QP release
- Long-term storage may require liquid Nitrogen
  - Segregation of products may require separate tanks
- Preparation may require class I safety cabinet to maintain sterility
Product Issues: Gene Therapy

- **Liquid formulations, stored frozen (<=-80ºC)**
  - Segregation of products

- **Like to be a Genetically Modified Organisms (GMO)**
  - Notification to HSE may be required
  - Risk assessment required
  - Preparation/reconstitution/dilution may require class I/II cabinets
Safety Issues

Potential and identified risks:
• Graft dysfunction and/or rejection
• Induction of autoimmunity or immunogenic reactions
• Induction of malignancies
• Transmission of infectious agents
• Potential for vector latency & reactivation
• Prolonged expression of transgene
X-linked Severe Combined Immunodeficiency (X-SCID)

Single gene mutation in the IL2RG gene, results in no functioning immune system
“Boy in bubble syndrome”

Gene therapy: risk of insertional mutagenesis, resulting in over-expression of proto-oncogene and development of leukaemia
Summary

- Specific requirements for ATMPs (traceability/GMP/GCP)
- Evolving Regulatory Landscape
- Multiple Regulators Involved
- Logistical Challenges
- Product Specific Issues
- Safety Issues and Unknown Risks