WHAT ARE ATMPs?

Clarifying misconceptions

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Why are we here?

Regulatory language can be difficult to understand.

This presentation attempts to clarify common misconceptions in what is classified as an ATMP.

By the end of this presentation we hope you will be able to:
- understand this schematic (atmpsveden.se)
- have the chance to ask questions

We start by breaking down the schematic...
Defining treatment modalities

What types of technologies are we discussing?

<table>
<thead>
<tr>
<th>Type of treatment/product modality</th>
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<td>Tissue Therapy Ø &gt; 100 µm</td>
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<td>Addition of tissues;</td>
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<td>• Autologous</td>
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<td>Cell Therapy Ø 10-50 µm</td>
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<td>• Genetic modification</td>
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<td>Vaccine</td>
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<td>Attenuated viruses, viral vectors,</td>
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<td>mAbs, mRNA</td>
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<tr>
<td>Biotech Ø 10 nm</td>
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<td>insulin, drug-antibody conjugates,</td>
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<td>fusion proteins</td>
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<tr>
<td>Chemicals Ø 1 nm</td>
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<td>Synthetic small or complex molecules</td>
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Not all ATMPs
By EMA legal classification all gene therapies are ATMPs
Synthetic oligonucleotides, legally speaking, are not gene therapies

Increasing complexity

Biologics

Medical Devices
Addition of non-biological structure
• Scaffolds
• Medical device

Tissue Therapy Ø > 100 µm
Addition of tissues;
• Autologous
• Allogeneic
• Xenogeneic

Cell Therapy Ø 10-50 µm
Addition of cells;
• Autologous
• Allogeneic
• Xenogeneic

Gene Therapy
Addition of;
• Recombinant genetic sequence
• Genetic modification

Vaccine
Attenuated viruses, viral vectors, mAbs, mRNA

Biotech Ø 10 nm
Recombinant proteins eg. mAbs, insulin, drug-antibody conjugates, fusion proteins

Chemicals Ø 1 nm
Synthetic small or complex molecules
Regulations around ATMPs

Medical Devices
Reg. EU 2017/45
Dir. 93/42/EEC (medical device)
Dir. 90/385/EEC (active implantable medical device)

Borderline hierarchy consideration GTMP > TEP > sCTMP

Type of treatment/product modality

Medical Devices
Tissue Therapy
Cell Therapy
Gene Therapy
Vaccine
Biotech
Chemicals

Combined ATMP (cATMP)
Tissue Engineered Product (TEP)
Somatic cell therapy medicinal product (sCTMP)
Gene Therapy Medicinal Product (GTMP)

Human transplants/tissues/cells

Advanced Therapy Medicinal Products (ATMP)
Reg. (EC) No 1394/2007 and Dir. 2009/120/EC

Biologics

Medicinal Product for human use
Reg. (EC) No 726/2004 and Dir. 2001/83/EC

ATMPs
NOT ATMPs

atmpsweden.se
Legal definition - Medicinal Product

a) any substance or combination of substances presented for treating or preventing disease in human beings; or
b) any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings.

Medicinal product for human use: most products Market authorization by EMA - Applicable for ATMPs
Medical Devices v combined ATMPs

Addition of non-biological structure - scaffolds/Medical device

Biologics

Medicinal Product for human use
Reg. (EC) No 726/2004 and Dir. 2001/83/EC

Type of treatment/product modality

Medical Devices
- Tissue Therapy
- Cell Therapy
- Gene Therapy

Biologics
- Advanced Therapy Medicinal Products (ATMP)
  Reg. (EC) No 1394/2007 and Dir. 2009/120/EC

Combined ATMP (cATMP)
- medical device
  plus a TEP, sCTMP or GTMP

Tissue Engineered Product (TEP)
- Somatic cell therapy medicinal product (sCTMP)
- Gene Therapy Medicinal Product (GTMP)
- Gene Therapies (GTMP)
- Medimun Product for human use
  Reg. (EC) No 726/2004 and Dir. 2001/83/EC

Vaccine
- Biotech
- Chemicals

Any medical device combined with a TEP, sCTMP or GTMP is a combined ATMP

Borderline hierarchy consideration
GTMP > TEP > sCTMP
Legal definition - Gene Therapy Medicinal Product (GTMP)

Annex I, part IV of Dir. 2001/83/E

Biological medicinal product with the following characteristics:

a) 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;

b) 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 diseases.
GTMP: in-vivo v ex-vivo

Borderline hierarchy consideration
GTMP > TEP > sCTMP

Cells gene modified in the lab and delivered to a patient are regulated as GTMP

CAR-T is an ex-vivo GTMP
Legal definition - Somatic Cell Therapy Medicinal Product (sCTMP)


- Substantially manipulated cells or tissues and/or not intended to be used for the same essential function(s) in donor and recipient;
- Administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action
Legal definition – Tissue Engineered Product (TEP)


• 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 tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices.
• Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, shall be excluded from this definition.
Legal definition – Combined ATMP (cATMP)


- It must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC, and

- its cellular or tissue part must contain viable cells or tissues, or

- its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.
# Tissues and cells v drug/device

### Medical Devices

- **Medical Devices**
  - Combined ATMP (cATMP)
    - medical device plus a TEP, sCTMP or GTMP

### Tissue Therapy

- **Tissue Engineered Product (TEP)**

### Cell Therapy

- **Somatic cell therapy medicinal product (sCTMP)**

### Gene Therapy

- **Gene Therapy Medicinal Product (GTMP)**

### Human transplants/tissues/cells

- **Human transplants/tissues/cells**

### Medicinal Product for human use

- **Biologics**
  - Vaccine
  - Biotech
  - Chemicals

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**Reg. (EC) No 1394/2007 and Dir. 2009/120/EC**

**Advanced Therapy Medicinal Products (ATMP)**

**regulated by member state’ NCA**
Why are cell based ATMPs different to traditional transplants?

Cells deemed to behave differently in the patient than donor due to;

• “substantial manipulation” (quality definition) and/or
• different essential function (clinical definition)
are regulated as ATMPs.

# Substantial v non-substantial manipulations

<table>
<thead>
<tr>
<th>Non-substantial manipulations</th>
<th>Substantial manipulations</th>
</tr>
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<tr>
<td>Cutting, Grinding, Shaping, Centrifugation</td>
<td>Sterilization, Vitrification, Soaking in Antibiotic or antimicrobial solution</td>
</tr>
<tr>
<td><strong>Cell expansion</strong> <em>(culture, ex-vivo)</em></td>
<td><strong>Differentiation and/or activation with growth factors</strong>*</td>
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Example of sCTMP—Apligraf

- Somatic Cell Therapy Medicinal Product

Primary mode of action for treating wound ulcer: secreting growth factors by transplanted tissue to support formation new skin by patient

Not a TEP
Example of a TEP – Holoclolar®

- Tissue Engineered Product
- Treat eye burns – EU MAA 2015
Example of a cATMP

- Combined Advanced Therapy Medicinal Product
  - sCTMP plus a medical device

Embryonic stem cells differentiated into pancreatic endoderm cells

Cells loaded into an immuno-protective device

Device transplanted subcutaneously into abdomen

- Cells mature in body, produce insulin
- Regulate glucose
- Eliminate the need for insulin therapy
- Reduce risk of hypo & hyperglycemic events
- Reduce long-term complications due to uncontrolled glycemia

http://viacyte.com/technology/stem-cell-engineering/
Can the same cells be an ATMP in one context and not in another?

- Yes!

- If the cells are not substantially manipulated but are used for a different essential function in the patient, they are classified as an ATMP.

- eg. to transplant bone marrow from a donor to patient bone marrow is not an ATMP but to administer that same bone marrow to the patient’s heart would now be considered an ATMP.

Figure adapted from: DJAC Crommelin et al. (eds), Pharmaceutical Biotechnology, 5th edition, Chapter 17-Advanced Therapies: Clinical, Non-clinical and Quality Considerations; K. Hoogendoorn
Advanced Therapy Medicinal Products (ATMP) (1394/2007)

- **Medical Devices**
  - Combined ATMP
    - medical device plus a TEP, sCTMP or GTMP

- **Biologics**
  - Type of treatment/product modality
    - Tissue Therapy
      - Tissue Engineered Product (TEP)
        - eg. Holoclar, Spherox, lab grown skin for burns treatment,
    - Cell Therapy
      - Somatic cell therapy medicinal product (sCTMP)
        - eg. Alofisel, lab expanded blood stem cells
    - Gene Therapy
      - Gene Therapy Medicinal Product (GTMP)
        - eg. CAR-T/Kymriah

- **Medical Product for human use**
  - Vaccine
  - Biotech
  - Chemicals

- **ATMPs**
  - eg. skin transplant for burns treatment
  - eg. bone marrow transplant, blood transfusions

- **NOT ATMPs**
  - eg. skin transplant for burns treatment

**Human transplants/tissues/cells, Blood**
Are de-cellularised tissues delivered to patients ATMPs?

It depends.

• NO
  • If no addition of cells – medical device
  • If re-cellularised with cells that have not been substantially manipulated and if the tissue is to be used for the same essential function (theoretically).

• YES
  • If re-cellularised with cells that are substantially manipulated.
  • If re-cellularised with cells that have not been substantially manipulated but the tissue is to be used for a different essential function (theoretically).
Advanced Therapy Medicinal Products (ATMP) (1394/2007)

**Type of treatment/product modality**

- **Medical Devices**
  - Combined ATMP: medical device plus a TEP, sCTMP or GTMP
    - eg. Holoclar, Spherox, lab grown skin for burns, P-TEV (Verigraft), recellularised tissues
  - eg. medical device only, decellularised scaffold

- **Tissue Therapy**
  - Tissue Engineered Product (TEP)
    - eg. Holoclar, Spherox, lab grown skin for burns

- **Cell Therapy**
  - Somatic cell therapy medicinal product (sCTMP)
    - eg. Alofisel, lab expanded blood stem cells

- **Gene Therapy**
  - Gene Therapy Medicinal Product (GTMP)
    - eg. CAR-T/Kymriah

- **Vaccine**

- **Biotech**

- **Chemicals**

**ATMPs**

- Human transplants/tissues/cells, Blood

**NOT ATMPs**

- eg. skin transplant for burns treatment
- eg. bone marrow transplant, blood transfusions

**ATMP Sweden**
Are recombinant technology vaccine products ATMPs/GTMPs?

Annex I, part IV of Dir. 2001/83/EC

• No.

• Recombinant technology vaccines eg. DNA vaccines/recombinant virus against infectious disease used to be classified as gene therapies, this was updated in the mid 2000s.

• Where the mechanism of action is intended to treat or prevent a viral infection these technologies are not classified as an ATMP.

• If a ’DNA vaccine’ or recombinant virus is intended to treat pathologies caused by the infection, for example malignancies, it is classified as an ATMP (GTMP).
### Advanced Therapy Medicinal Products (ATMP) (1394/2007)

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#### ATMPs
- eg. medical device only, decellularised scaffold
- eg. skin transplant for burns treatment
- eg. bone marrow transplant, blood transfusions

#### NOT ATMPs
- eg. medical device only, deccellarised scaffold
- eg. stem cells
- eg. CAR-T/Kymriah

**ATMP Sweden**

- eg. Attenuated viruses, viral vectors, mAbs, mRNA
- eg. skin transplant for burns treatment
- eg. bone marrow transplant, blood transfusions

**Human transplants/tissues/cells, Blood**
Can recombinant bacteria being delivered to a patient be a GTMP?

Yes!

• For example, bacteria genetically engineered and delivered to a patient to secrete recombinant therapeutic protein is regulated as a GTMP.
• The classification in this case is that the recombinant nucleic acid administered to human beings adds a genetic sequence that has the direct therapeutic effect.
• While the product does not modify the DNA of the patient or secrete therapeutic RNA, it is still legally classified as a gene therapy.
Can recombinant mRNAs be ATMP/GTMPs?

Yes!

- If the mRNA is produced from a recombinant source eg. linearised plasmid, and the resultant mRNA will be delivered to patients with a mechanism of action based on the mRNA or protein translated from it.

### Advanced Therapy Medicinal Products (ATMP) (1394/2007)

**Medical Devices**
- Combined ATMP: medical device plus a TEP, sCTMP or GTMP
- Medical Devices only
- Medical device, decellularised scaffold

**Biologics**
- Tissue Therapy
- Cell Therapy
- Gene Therapy
- Vaccine
- Biotech
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**Type of treatment/product modality**

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**Human transplants/tissues/cells, Blood**
- eg. skin transplant for burns treatment
- eg. bone marrow transplant, blood transfusions

**ATMPs**
- Human transplants/tissues/cells, Blood

**NOT ATMPs**
- eg. medical device only, decellularised scaffold

ATMP Sweden
Are synthetic oligonucleotide-based products ATMP/GTMPs?

No

• Legally synthetic oligonucleotide-based medicines are not classified as gene therapies.
• Legally only those products with active substances based on recombinant DNA technologies that are delivered to patients to add or regulate gene sequences are gene therapies.
• Though synthetically produced oligonucleotides are widely referred to as gene therapies, they are better described as complex small molecule medicinal products or nucleotide based medicines.
Advanced Therapy Medicinal Products (ATMP) (1394/2007)

Type of treatment/product modality

- **Medical Devices**
  - Tissue Therapy
    - Tissue Engineered Product (TEP)
      - eg. Holoclar, Spherox, lab grown skin for burns treatment, P-TEV (Verigraft), recellularised tissues
  - Cell Therapy
    - Somatic cell therapy medicinal product (sCTMP)
      - eg. Alofisel, lab expanded blood stem cells
  - Gene Therapy
    - Gene Therapy Medicinal Product (GTMP)
      - eg. CAR-T/Kymriah, ILP100, in-vitro transcribed mRNA

- **Biologics**
  - Vaccine
    - eg. Attenuated viruses, viral vectors, mAbs, mRNA
  - Biotech
    - eg. Spinraza, Patisiran, Givosiran
  - Chemicals
    - Synthetic oligonucleotide, legally speaking, are not gene therapies

- **ATMPs** (Combined ATMP medical device plus a TEP, sCTMP or GTMP)
  - eg. medical device only, decellularised scaffold

- **NOT ATMPs**
  - Human transplants/tissues/cells, Blood
    - eg. skin transplant for burns treatment, eg. bone marrow transplant, blood transfusions

By EMA legal classification all gene therapies are GTMPs
Are Extracellular vesicles (EVs) ATMPs?

It depends

• If the product is EVs purified from non-modified cells or from genetically modified cells, but where the vesicles contain only functional transgenic protein, they are not ATMPs, but biologics.
• If the EVs contain functional transgenic mRNAs that will perform the intended therapeutic function in the patient they are classified as ATMPs (i.e. GTMPs).
Advanced Therapy Medicinal Products (ATMP) (1394/2007)

- **Medical Devices**
  - Combined ATMP medical device plus a TEP, sCTMP or GTMP
  - eg. medical device only, decellularised scaffold

- **Tissue Therapy**
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    - eg. Holoclar, Spherox, lab grown skin for burns treatment, P-TEV (Verigraft), recellularised tissues

- **Cell Therapy**
  - Somatic cell therapy medicinal product (sCTMP)
    - eg. Alofisel, lab expanded blood stem cells

- **Gene Therapy**
  - Gene Therapy Medicinal Product (GTMP)
    - eg. ILP100, in-vitro transcribed mRNA, EV with recombinant mRNA

- **Vaccine**
  - eg. Attenuated viruses, viral vectors, mAbs, mRNA

- **Biotech**
  - eg. EV with transgenic protein

- **Chemicals**
  - eg. Spinraza, Patisiran, Givosiran

By EMA legal classification all gene therapies are GTMPs

Synthetic oligonucleotide, legally speaking, are not gene therapies

ATMPs

NOT ATMPs

Human transplants/tissues/cells, Blood

ATMP Sweden
And the final schematic...

Find updated information and more at;
https://atmpsweden.se/resources/what-are-atmps/
### Medical Devices
Reg. EU 2017/45
Dir. 93/42/EEC
Dir. 90/385/EEC

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**ATMPs**

**NOT ATMPs**

[atmpsweden.se](http://atmpsweden.se)
Why is it important these classifications are understood?

So developers know what regulations they need to follow.

Applications to CAT for scientific recommendation/classification of **borderline products** are strongly recommended to be sure


**MPA:** [https://www.lakemedelsverket.se/en/permission-approval-and-control/advisory/regulatory-advice](https://www.lakemedelsverket.se/en/permission-approval-and-control/advisory/regulatory-advice)
Thanks for taking this journey with us!...questions/discussion

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