The EU Regulatory Framework for the ATMP

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• The views expressed here are my personal views, and may not be understood or quoted as being made on behalf of EMA or reflecting the position of the EMA”.
Legal framework in Europe

- EU law: The Regulation 1394/2007/EC
  - Definitions
  - Classification procedure
- European Medicinal Agency (EMA) guidelines
- National Agency guidelines

Legal status of the Advanced Therapy Medicinal Products (ATMP)

- Regulation 1394/2007/EC
- This Regulation is a *lex specialis*, which introduces additional provisions to those laid down in Directive 2001/83/EC.
- The scope of this Regulation should be to regulate advanced therapy medicinal products which are intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process, in accordance with the general scope of the Community pharmaceutical legislation laid down in Title II of Directive 2001/83/EC.
Biologicals and ATMP

• After nearly 15 years, biologicals development is considered common practice, however as manufacturing get more complex, the risk perception is increased.

• Advanced Therapy Medicinal Products in the EU are a sub class of the biologicals which on the basis of the complexity have been dedicated a specific law (Regulation 1394/2007/EC).
Regulation 1394/2007/EC

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Article 2 Definitions

(a) ‘Advanced therapy medicinal product’ means any of the following medicinal products for human use:

— a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,

— a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,

— a tissue engineered product as defined in point (b).

Containing the Annex I of 2001/83/EC revision

2.1. **Gene therapy medicinal product**

Gene therapy medicinal product means a biological medicinal product which has 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.
SOMATIC CELL THERAPY MEDICINAL PRODUCTS
(HUMAN AND XENOGENEIC) Dir 2009/120/EC

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.

Article 2  Definitions

(b) ‘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 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.
Article 2  Definitions

(c) Cells or tissues shall be considered ‘engineered’ if they fulfil at least one of the following conditions:
— the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations,
— the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

Annex I  Manipulations referred to in the first indent of Article 2(1)(c)

— cutting,
— grinding,
— shaping,
— centrifugation,
— soaking in antibiotic or antimicrobial solutions,
— sterilization,
— irradiation,
— cell separation, concentration or purification,
— filtering,
— lyophilization,
— freezing,
— cryopreservation,
— vitrification.
Article 2   Definitions

(d) ‘ Combined advanced therapy medicinal product’ means an advanced therapy medicinal product that fulfils the following conditions:

— 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

Article 8   Evaluation procedure for the MAA

1. The Committee for Medicinal Products for Human Use shall consult the Committee for Advanced Therapies on any scientific assessment of advanced therapy medicinal products necessary to draw up the scientific opinions (...)
2. When preparing a draft opinion for final approval by the Committee for Medicinal Products for Human Use, the Committee for Advanced Therapies shall endeavour to reach a scientific consensus. (....)
5. The Agency shall draw up specific procedures for the application of paragraphs 1 to 4.
Competent Authority for Marketing Authorization

An Agency of the European Union

To foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health

- Network of European experts (+3500)
- 6 Scientific Committees (CHMP, CAT, COMP, PDCO, CVMP, HMPC & …)
- Over 15 working parties (human unit)
- CP (for ATMPs): 1 single market
- Motto: Science, Medicines, Health
- Values: Europe, public health, innovation, sense of purpose, quality, transparency, integrity, honesty, objectivity, impartiality
European Structure
A dedicated committee at EMA

CAT
Chair: P. Salmikangas

CHMP Co-ordinator responsible for flow of information between CAT & CHMP + discussion/adoption of opinion at CHMP

Peer review by 1 CHMP member 1 (or more) CAT member(s)

Cat (Co)Rapp coordinate procedure & discussions at CAT + prepare draft opinions and assessment reports

CHMP Co-ordinator (at CHMP level) + CAT Co-Rapport (at CAT level)

ASSESSMENT
TEAM 1
CHMP Co-ordinator (at CHMP level) + CAT Co-Rapport (at CAT level) incl. Q/S/E Experts

ASSESSMENT
TEAM 2
CHMP Co-ordinator (at CHMP level) + CAT Co-Rapport (at CAT level) incl. Q/S/E Experts
Article 9 Combined advanced therapy medicinal products

1. Where a combined advanced therapy medicinal product is concerned, the whole product shall be subject to final evaluation by the Agency.

2. The application for a marketing authorisation for a combined advanced therapy medicinal product shall include evidence of conformity with the essential requirements referred to in Article 6.

3. The application for a marketing authorisation for a combined advanced therapy medicinal product shall include, where available, the results of the assessment by a notified body in accordance with Directive 93/42/EEC or Directive 90/385/EEC of the medical device part or active implantable medical device part.
**Article 9 Combined advanced therapy medicinal products**

- The Agency shall recognise the results of that assessment in its evaluation of the medicinal product concerned.
- The Agency may request the relevant notified body to transmit any information related to the results of its assessment. The notified body shall transmit the information within a period of one month.
- If the application does not include the results of the assessment, the Agency shall seek an opinion on the conformity of the device part with Annex I to Directive 93/42/EEC or Annex 1 to Directive 90/385/EEC from a notified body identified in conjunction with the applicant, unless the Committee for Advanced Therapies advised by its experts for medical devices decides that involvement of a notified body is not necessary.

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**Article 16 Scientific advice**

1. The applicant or holder of a marketing authorisation may request advice from the Agency on the design and conduct of pharmacovigilance and of the risk management system referred to in Article 14.

2. By way of derogation from Article 8(1) of Council Regulation (EC) No 297/95 of 10 February 1995 on fees payable to the European Agency for the Evaluation of Medicinal Products (1), a 90 % reduction for small and medium-sized enterprises and 65 % for other applicants shall apply to the fee for scientific advice payable to the Agency for any advice given in respect of advanced therapy medicinal products pursuant to paragraph 1 of this Article and Article 57(1)(n) of Regulation (EC) No 726/2004.
Article 17 Scientific recommendation on advanced therapy classification

• Any applicant developing a product based on genes, cells or tissues may request a scientific recommendation of the Agency with a view to determining whether the referred product falls, on scientific grounds, within the definition of an advanced therapy medicinal product.

• The Agency shall deliver this recommendation after consultation with the Commission and within 60 days after

ATMP Classification Procedure

• “Companies can apply to the European Medicines Agency to determine whether a medicine they are developing is an advanced-therapy medicinal product (ATMP). The procedure allows them to receive certification that a medicine, based on genes, cells or tissues, meets the scientific criteria that define ATMPs.”


• It is unique and the Regulation allows only to say if a medicinal product is or not an ATMP.
Classification

• In relation to microvesicles, a previous judgment was delivered on 2009-12-04 on "mesenchymal stem cell-derived microvesicles (containing receptors, proteins, lipids, mRNA and microRNA) intended for treatment of renal diseases NOT (being) an advanced therapy medicinal product".

• Is this judgement valid for all class of microvesicles? Uncertain.
• Would they be classified as Medicinal Product? Likely as Biologicals.

Classification

• In relation to RBC loaded with chemioterapics, a previous judgment was delivered on NOT (being) an advanced therapy medicinal product".

• Is this judgement valid for all class of cells loaded with a NCE? Uncertain.
• Would they be classified as Medicinal Product? Likely as NCE.
Classification

- In relation to Genetically modified *Lactococcus lactis* secreting human interleukin-10 intended for treatment of inflammatory bowel disease, a previous judgment was delivered on them
- *being an advanced therapy medicinal product and specifically a Gene Therapy Medicinal Product.*
- Is this judgement valid for all class of bacteria or yeast? Uncertain but unlikely.

Classification

- Finished product: Suspension of platelets produced *in vitro*
- Proposed indication: Haematology
- On the basis that: - Platelets are not considered cells for ATMP classification purposes as they are anucleate
- EMA/CAT considers that the Product does **NOT** to fall within the definition of an Advanced Therapy Medicinal Product.
Article 18 Certification of quality and non-clinical data

• Small and medium-sized enterprises developing an advanced therapy medicinal product may submit to the Agency all relevant quality and, where available, non-clinical data required in accordance with modules 3 and 4 of Annex I to Directive 2001/83/EC, for scientific evaluation and certification.

ATMP Data Certification

• As an incentive to conduct those studies, a system of evaluation and certification of the resulting data by the Agency, independently of any marketing authorization application, should be introduced.
• Even though the certification would not be legally binding, this system should also aim at facilitating the evaluation of any future application for clinical trials and marketing authorization application based on the same data.
ATMP Data Certification


Article 15  Traceability

1. The holder of a marketing authorisation for an advanced therapy medicinal product shall establish and maintain a system ensuring that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private practice where the product is used.

2. The hospital, institution or private practice where the advanced therapy medicinal product is used shall establish and maintain a system for patient and product traceability. That system shall contain sufficient detail to allow linking of each product to the patient who received it and vice versa.

3. Where an advanced therapy medicinal product contains human cells or tissues, the marketing authorisation holder, as well as the hospital, institution or private practice where the product is used, shall ensure that the traceability systems established in accordance with paragraphs 1 and 2 of this Article are complementary to, and compatible with, the requirements laid down in Articles 8 and 14 of Directive 2004/23/EC as regards human cells and tissues other than blood cells, and Articles 14 and 24 of Directive 2002/98/EC as regards human blood cells.
Cell & Tissue clinical use is regulated by National Competent Authorities

Directive 2004/23/EC

on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells


The procurement of tissue and cells as raw materials for the production of Cell based Advanced Therapy Medicinal Product Are regulated according the prescription of these Directives. The traceability has to be harmonized.

Article 15 Traceability

4. The marketing authorisation holder shall keep the data referred to in paragraph 1 for a minimum of 30 years after the expiry date of the product, or longer if required by the Commission as a term of the marketing authorisation.

5. In case of bankruptcy or liquidation of the marketing authorization holder, and in the event that the marketing authorization is not transferred to another legal entity, the data referred to in paragraph 1 shall be transferred to the Agency.

6. In the event that the marketing authorisation is suspended, revoked or withdrawn, the holder of the marketing authorization shall remain subject to the obligations laid down in paragraphs 1, 3 and 4.

7. The Commission shall draw up detailed guidelines relating to the application of paragraphs 1 to 6, in particular the type and amount of data referred to in paragraph 1.
Art 28 “Hospital use”

- in Article 3, the following point shall be added:
- Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.


a) Single access through a EU portal
b) Assessment coordinated by a “reporting Member State”

c) Max of 50 day of additional time for the ATMP
d) National Ethical Board approval
Support for ATMP development

a) Institutional support
   a) TTO offices,
   b) Translational support Offices
   c) Non profit Investors
b) Competent Authorities support
   a) Scientific advice
   c) European Research Infrastructures support
      a) EATRIS, ECRIN, BBMRI
d) Foundations
   a) Non profit investments or funding
e) Industry
      a) For profit investments; Public-Private Partnership

And when you have a past?
Previous work

• Enquire for the IP position
• Enquire for the Translation Potential (EATRIS-inside)
• Enquire for possible investors
• Ask for scientific advice on the regulatory position for Marketing Application of the previous work

Conclusion

All roads lead to Rome ..... 

and you could travel them in many different ways ........... just avoid the donkey.
Thanks for your attention