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Vector-based ATMP development in the EU
Regulatory and scientific considerations

Ilona Reischl, PhD

AGES MEA, Austria

Institute Surveillance

Disclaimer

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- **EMA**: “The views expressed in this presentation are my personal views and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.”

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Advanced Therapy Medicinal Products

Legislation

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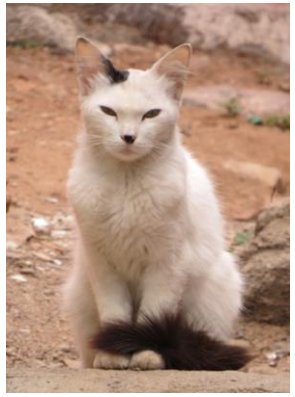
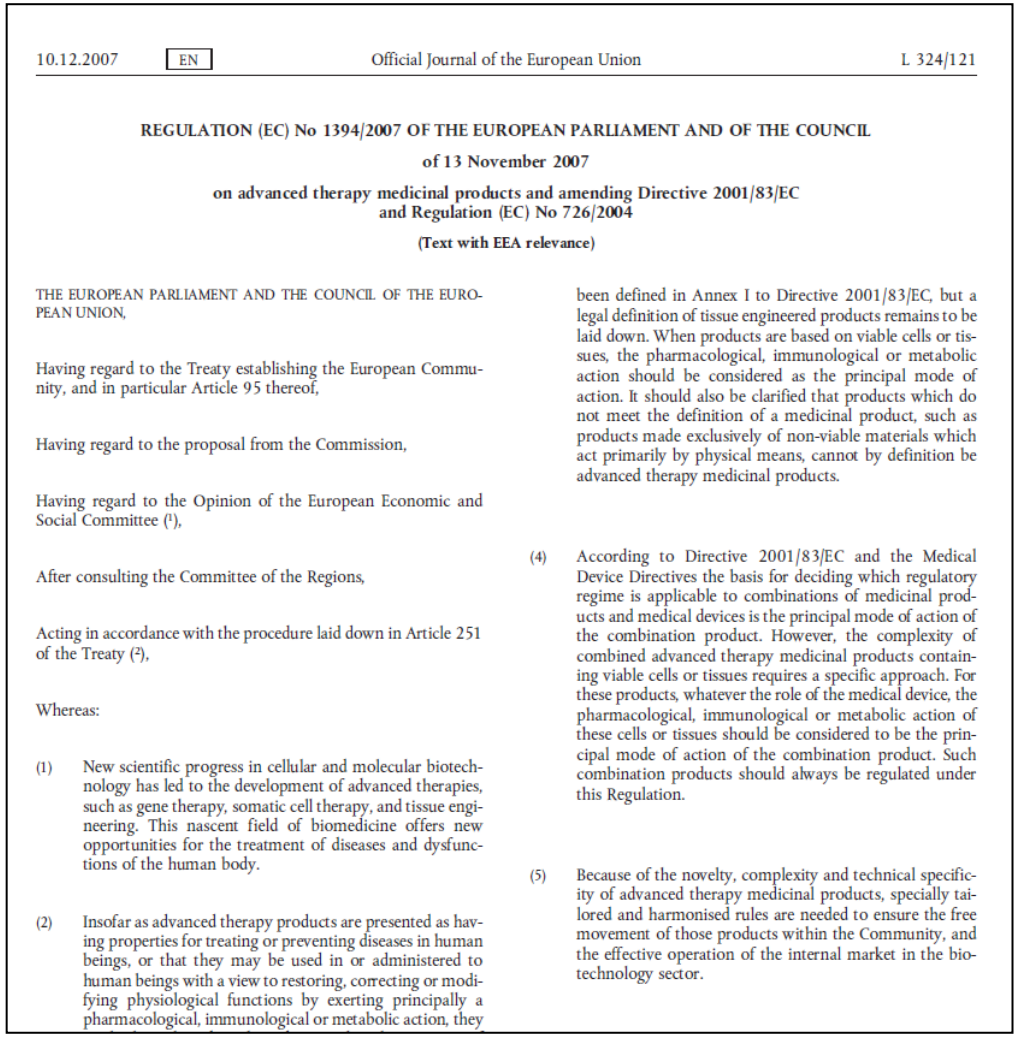
Regulation (EC) No 1394/2007

Effective since
30 December 2008
'Lex specialis'

CAT





10.12.2007 EN Official Journal of the European Union L 324/121

REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

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 Social Committee (1),

After consulting the Committee of the Regions,

Acting in accordance with the procedure laid down in Article 251 of the Treaty (2),

Whereas:

(1) New scientific progress in cellular and molecular biotechnology has led to the development of advanced therapies, such as gene therapy, somatic cell therapy, and tissue engineering. This nascent field of biomedicine offers new opportunities for the treatment of diseases and dysfunctions of the human body.

(2) Insofar as advanced therapy products are presented as having properties for treating or preventing diseases in human beings, or that they may be used in or administered to human beings with a view to restoring, correcting or modifying physiological functions by exerting principally a pharmacological, immunological or metabolic action, they 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.

(4) According to Directive 2001/83/EC and the Medical Device Directives the basis for deciding which regulatory regime is applicable to combinations of medicinal products and medical devices is the principal mode of action of the combination product. However, the complexity of combined advanced therapy medicinal products containing viable cells or tissues requires a specific approach. For these products, whatever the role of the medical device, the pharmacological, immunological or metabolic action of these cells or tissues should be considered to be the principal mode of action of the combination product. Such combination products should always be regulated under this Regulation.

(5) Because of the novelty, complexity and technical specificity of advanced therapy medicinal products, specially tailored and harmonised rules are needed to ensure the free movement of those products within the Community, and the effective operation of the internal market in the biotechnology sector.

Cell Therapy Medicinal Products
Dir/2001/83/EC

Gene Therapy Medicinal Product
Dir/2001/83/EC

Tissue Engineered Products

Combined ATMPs

GMP for ATMPs

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→ Eudralex Volume 4

https://ec.europa.eu/health/documents/eudralex/vol-4_en

EudraLex
The Rules Governing Medicinal Products in the European Union
Volume 4
Good Manufacturing Practice

Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2017_11_22_guidelines_gmp_for_atmps.pdf

Conduct of clinical trials

New Legislation/Process/Database going live 2022

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REGULATION (EU) No 536/2014

- Approval of clinical trials remains remit of National Competent Authorities
- Joint process between member states
- Single opinion per member state (ethics committee and agency)
- New database

- EudraLex - Volume 10 - Clinical trials guidelines: https://ec.europa.eu/health/documents/eudralex/vol-10_en

Interfacing legislation (CMC)

Clinical trial approval is remit of EU member states

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Development/Clinical trial stage	Licensing stage	Post approval

Genetically modified organism (GMO) legislation

Medical device legislation
(integral/non-integral co-packaged/referenced medical device); May 2021

In vitro diagnostics legislation
(IVD/Companion diagnostic CDx); May 2022

GMO framework

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- Approval by GMO authorities is required during the clinical trial stage → https://ec.europa.eu/health/human-use/advanced-therapies_en

- GMO requirements are addressed in the marketing authorization procedure
- → specific environmental risk assessment; Consultation of EU GMO authorities
- Use of the medicinal product in accordance with the SmPC is therefore compliant with the GMO framework

EMA Q&A 3.3.5. What should I submit if my medicinal product contains or consists of genetically modified organisms? (Rev 2020)

www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pre-authorisation-guidance#3.3-quality-section

ATMPs and medical devices

Not all ATMP device combinations are „combined ATMPs“

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Combined ATMP according to ATMP Regulation definition

- ATMP has one or more **integral** medical devices (MDs) or active implantable MDs components in scope the EU medical device legislation (integral - single integral product, intended exclusively for use in the given combination, not reusable)

  example: viral vector in prefilled syringe

ATMP with non-integral devices (co-packaged, referenced) ≠ combined ATMP

- A medicinal product(s) with integral and/or non-integral medical device(s) necessary for administration, correct dosing or use of the drug product (draft Guideline on the quality requirements for drug-device combinations

  example: ATMP with a refillable co-packaged delivery device

Integral device combinations for ATMPs

.. at MAA

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- Article 9 REG (EC) No 1394/2007 applies to combined ATMPs → dedicated CAT/Notified Body procedure
- Information on medical devices used during surgical procedures for application, implantation or administration of an ATMP which may impact on efficacy or safety as per Annex I, Part IV, Section 5.2.1 of Annex Dir2001/83/EC is expected in **Module 5**
- Article 117 of the MDR (requirement for a Notified Body Opinion) does not apply to ATMPs → consultation procedure for non-ATMPs

- The Guideline on the quality requirements for drug-device combinations (draft) can be considered where it is more specific than dedicated ATMP guidelines

At MAA - Requirement for Release testing in the EU

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EMA/354272/2019

"Questions and answers on the exemption from batch controls carried out on ATMPs imported into the European Union from a third country"

www.ema.europa.eu/en/documents/other/questions-answers-exemption-batch-controls-carried-out-atmps-imported-european-union-third-country_en.pdf

- The exemption from re-testing batches upon import into the EU for ATMPs may only be granted where the conditions laid down in paragraph 11.17 of the EU GMP guideline for ATMPs are met, specifically:
  1. limited amount of material available; or
  2. short shelf-life; and
  3. testing in the 3rd country should be conducted in GMP-certified facilities

  Justifications would have to specifically address these points → designed for autologous products, requirements are difficult to fulfill for products where the viral vector is the active substance

Gene therapy medicinal product

Legal definition DIR/2009/120/EC

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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.

Prerequisite for ATMP classification – biological medicinal product → Synthetically manufactured nucleic acids cannot be considered as GTMPs vaccines against infectious diseases also excluded

Classification

of vector-based products

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- Gene therapy
  - Vector is the active substance, e.g. recombinant nucleic acid and viral or non-viral vector to replace/repair/replace/add/delete a sequence
  - In vivo genome editing – active substance(s) - tools for editing e.g. rec. nucleic acid, rec. protein, synth. oligonucleotide/RNA, ribonucleoprotein and viral/non-viral vectors
  - Vector is used to generate the active substance, e.g. CAR T cells ← starting material

- Somatic cell therapy/tissue engineered product
  - Where the genetic modification of the cell is not related to the therapeutic, prophylactic or diagnostic effect of the product, e.g. introduction of a suicide gene ← starting material

→ What are the requirements for starting material in the EU?

Vectors/plasmids

as starting materials

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GMP for ATMPs

- In the case of vectors and naked plasmids used as starting materials for the manufacturing of gene therapy medicinal products, the **principles of GMP** apply from the bank system used to manufacture the vector or plasmid used for gene transfer.

→starting materials are not under full GMP

→The same level of information needed in the dossier as for vector as active substance

- Question and Answer document in preparation to illustrate requirements, e.g. principles of GMP → Risk based approach to starting material qualification

Vectors/Plasmids

as starting materials

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- Genome editing tools used ex-vivo to generate genetically modified cells are also considered as starting materials
- For in vitro-transcribed (m)RNAs used as active substances, the linearized template plasmid DNA should be considered as starting material
- Complexing materials for formulating drug substance are considered as starting materials. Level of information required will depend on nature of the complexing material and resulting DS.

- *(Draft)* Guideline on quality, non-clinical and clinical requirements for investigational ATMPs in clinical trials *(finalization delayed due to Brexit/pandemic)*

Scientific challenges

General points

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Most current vector-based products are in areas of high unmet medical need →
High pressure, accelerated development →

- Develop analytical tools early, particularly potency assays
- Explore (sources of) variability (cell-based products)
- Starting-/ raw material qualification
- Avoid mixing process changes and changes to analytical tools
- Keep sufficient pre-change material for comparability exercise
- Maintain link to earlier non-clinical/clinical data (representativeness)
- Stringency of the comparability exercise depends on maturity of development (exploratory vs pivotal)

Scientific challenges

Insertional mutagenesis

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Reflection paper on clinical risks deriving from insertional mutagenesis (EMA/CAT/190186/2012)

- Replication deficient viral vectors → replication deficiency to be demonstrated for DS and, where appropriate, intermediates, as well as any packaging/producer cell lines
- Genetically-modified cells → RCV testing at DS or other intermediate levels is not required, provided that absence of RCVs is demonstrated at virus starting material and RCV formation during manufacturing can be excluded
- Replication competent viral vectors or replication-conditional viral vectors → clear rationale for construct and individual genetic elements that control replication to be provided on its safe use for the proposed clinical indications.

Scientific challenges

Analytics

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- Develop the potency assay(s) early!
- Relevant parameters for gene therapies
  - Titer/infectivity
  - mRNA expression
  - Functional protein
- Where a surrogate assay is intended to be used, generate sufficient proof of concept for acceptance, already for exploratory studies

- Considering that most current vector-based products raise immunogenicity and re-treatment is questionable → High expectation for quality already for exploratory clinical trials

Scientific challenges

Comparability

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Relevant aspects:

- compliance with approved specifications
- extended characterization
- assessment of critical control points in the manufacturing process
- stability data from accelerated or stress conditions
- potential differences in product-related substances and product-related impurities, including potentially co-packaged host cell DNA
- Historical data to provide insight into potential “drifts” of quality attributes with respect to safety and efficacy

→ Q&A on comparability considerations for ATMPs

EU Guidance

.. For vector based products – Quality (selection)

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- (Draft) Guideline on quality, non-clinical and clinical requirements for investigational ATMPs in clinical trials (EMA/CAT/852602/2018)
- Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014) revised 2018
- Q&A on comparability considerations for ATMPs (EMA/CAT/499821/2019)
- Reflection paper on design modifications of gene therapy medicinal products during development (EMA/CAT/GTWP/44236/2009)
- Reflection paper on quality, non-clinical and clinical issues relating specifically to recombinant adeno-associated viral vectors (CHMP/GTWP/587488/07)
- Guideline on non-clinical testing for inadvertent germline transmission of the gene transfer vectors (EMEA/273974/2005)
- Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (CAT/CHMP/GTWP/671639/2008)
- Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products (CHMP/GTWP/125491/06)
- Pharm. Eur. 5.14 “Gene transfer medicinal products for human use”

Thank you for your attention
Questions?