



**HAL**  
open science

## **A Booklet of I-BioLex posters**

Aurélie Mahalatchimy, Valentin Roby

► **To cite this version:**

| Aurélie Mahalatchimy, Valentin Roby. A Booklet of I-BioLex posters. 2025. ⟨halshs-05365079⟩

**HAL Id: halshs-05365079**

**<https://shs.hal.science/halshs-05365079v1>**

Submitted on 14 Nov 2025

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY 4.0 - Attribution - International License

**A booklet  
of *I-BioLex*  
posters**



I-BioLex “Fragmentation and defragmentation of the law on biomedical innovations” is a research project funded by the French National Agency (ANR-22- CE41-0012-03; PI: A. Mahalatchimy, CNRS-Aix-Marseille University DICE, CERIC, Aix-en-Provence, France) from 1<sup>st</sup> January 2021 to 30 June 2026.

From 1<sup>st</sup> January 2021 to 31 October 2025, the I-BioLex members and other colleagues have produced 26 posters that have been presented in International and European congresses in France and abroad. These posters are parts of the analysis conducted on fragmentation (division or segmentation), and defragmentation (gathering together, connecting or ‘harmonising’) of the European law on Biomedical innovations, regarding biological medicines and their subcategories, Advanced Therapy Medicinal Products and their subcategories, and orphan medicines. They relate to the various topics presented below in the table of contents.

**More information on the I-BioLex research project can be found on ELSIBI [here](#)**

24 October 2025

Authors: Aurélie Mahalatchimy and Valentin Roby



# Table of Contents

## I. Quality aspects/Manufacturing

Comparative quality aspects of gene therapy medicinal products and medicinal products containing genetically modified cells **6**

Production Aspects of Advanced Therapy Medicinal Products **8**

Quality Control and Batch Release Aspects of Advanced Therapy Medicinal Products **10**

What are the quality challenges regarding comparability considerations of advanced therapy medicinal products? **12**

Production of ATMPs: What are the specificities for quality aspects? **14**

The challenges of Advanced Therapy Medicinal Products manufacturing in the European Union: Strengths and limits of current regulatory tools **16**

## II. Clinical aspects

What specificity for the clinical aspects of investigational advanced therapy medicinal products? **20**

Specific guidelines requirements for clinical trials with Advanced Therapy Medicinal Products in the European Union **22**

## III. Market Access/Hospital Exemption

The Marketing Authorisation of Advanced Therapy Medicinal Products in the European Union **26**

Expediting marketing authorization pathways for patients' access to advanced therapies **28**

What regulatory pathways for health technologies using both medical devices and T&C in the European Union? **30**

ATMPs: exceptional manufacturing returns to the patient's bedside **32**

## IV. Health Technology Assessment/ Cost issues

The new European regulation on Health Technology Assessment: what changes for Advanced Therapy Medicinal Products? **36**

The European regulation on Health Technology Assessment: balancing European and national levels **38**

Contracts for better access to Advanced Therapy Medicinal Products **40**

Real access to ATMPs: the cost issue **42**

## **V. Orphan Medicines**

Improving access to innovative medicines: proposals from national authorities to revise the European legislation **46**

The current revision of the orphan medicinal products regulation in the European Union: what is at stake for gene and cell therapy? **48**

## **VI. Actors**

Which actors to influence the adoption of EU guidelines for Advanced Therapy Medicinal Products? **52**

Comparing actors participating in the adoption process of SoHO and ATMP regulations at the European level **54**

An exploratory analysis on the involvement of European organisations in the field of biomedical innovation **56**

Innovative therapy in European Parliament's positions: a numerical science-based vocabulary analysis **58**

Mapping regulators' early interactions procedures to support innovation **60**

A comparative study of national schemes and services for "early interaction" with Regulators **62**

## **VII. Guidance**

Mapping the ATMPs Guidance Landscape **66**

## **VIII. French policy**

Organoids and organs-on-chip in gene and cell therapy: which innovation strategies in France? **70**

**I**

**Quality aspects/  
Manufacturing**

## Comparative quality aspects of gene therapy medicinal products and medicinal products containing genetically modified cells

**A. MAHALATCHIMY, E. GENNET, V. ANDRIEU, M. FERAUD, V. LACAILLE, J. VÉRAN, F. SABATIER, M. MORRISON**, Comparative quality aspects of gene therapy medicinal products and medicinal products containing genetically modified cells, Annual Conference of the European Association of Health Law, Ghent, Belgium, 20-22 April 2022 (POSTER available at <https://shs.hal.science/halshs-03779383v1>)

### Abstract

The European Medicines Agency has recently revised its guidelines on quality, non-clinical and clinical aspects of Gene Therapy Medicinal Products (GTMPs text) and of medicinal products containing genetically modified cells (GMCMPs text), respectively in 2018 for the former and in 2020 for the latter. The latest revision has been particularly justified by the new developments in genome editing techniques, especially the wide use of the CRISPR-Cas technique, and with T-cells. Gene therapy medicinal product (GTMP) is a legal sub-category of medicines among Advanced Therapy Medicinal Products (ATMPs). However, medicinal product containing genetically modified cells (GMCMP) is not explicitly mentioned as a legal subcategory under EU regulation n°1394/2007 on ATMPs. Nevertheless, both GTMPs and GMCMPs should be considered as ATMPs under European Union Law. On the one hand, quality issues have been raised for all ATMPs regarding the reproducibility of the manufacturing process given the variable character of the starting materials. On the other hand, there is an overlap in the scope of the aforementioned guidelines when medicinal products containing genetically modified cells are to be considered gene therapy medicinal products. What are the similarities and differences between the quality of gene therapy medicinal products and the quality of medicinal products containing genetically modified cells while both are ATMPs? This poster is based on a comparative analysis of the quality sections of the two above-mentioned texts. In a first systematic approach, we identified the similarities and the specificities of texts outline (sub-section titles). Then, we analysed contents through the establishment of 3 types of comparative tables using color codes: common titles, different titles with similar contents, different titles with different contents in order to highlight similarities and specificities regarding the quality requirements between these two kinds of medicinal products when they are intended for use in humans and presented for marketing authorization applications.



## Production Aspects of Advanced Therapy Medicinal Products

J. VÉRAN, F. SABATIER, M. MORRISON, C. LE CORRE, C. S. PEIXOTO, E. GENNET, V. ANDRIEU, A. MAHALATCHIMY, Production Aspects of Advanced Therapy Medicinal Products, Annual Conference of the European Association of Health Law, Ghent, Belgium, 20-22 April 2022 (POSTER available at <https://archivesic.ccsd.cnrs.fr/AO-DROIT/halshs-03779408v1>)

### Abstract

Background : Good Manufacturing Practice (GMP) guidelines established by the European Commission are essential to ensure quality, safety and efficacy of medicinal products. Guidelines are designed to address specific risks of medicinal products and as such, are continuously being adapted. Advanced Therapy Medicinal Products (ATMPs) are medicinal products that have been regulated in the European Union from 2007 to cover the emerging field of genes, tissues or cell-based therapies. Dedicated GMP guidelines for ATMPs are enforceable since 2017. Consequently, GMP guidelines covering manufacture of biological active substances and medicinal products for human use including biological active substances (hereafter “Biologicals”) have been revised in June 2018 with the objective to prevent overlapping scope. Research question and methods: Our hypothesis is that the biological nature that commonly characterize ATMPs and biologicals may sustain a large body of similarities in the manufacturing aspects as addressed by the respective guidelines. We aim to comparatively analyze the two following texts : Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products, and Manufacture of Biological active substances and Medicinal Products for human use including biological active substances. Focus has been given on manufacturing, i.e. production recommendations including personnel, premises, equipment, documentation, starting and raw materials, seed lot and cell bank systems. In a systematic approach we highlighted similarities and specificities in the text outlines (paragraph and section titles). Then content has been comparatively investigated based on chosen relevant key words found in both texts (production, operation principles, production area, facilities, cross contamination in production, environmental monitoring and specifications, starting and raw materials).

## Production Aspects of Advanced Therapy Medicinal Products

Julie Véran<sup>1</sup>, Florence Sabatier<sup>2</sup>, Michael Morrison<sup>3</sup>, Carla Le Corre<sup>4</sup>, Carlota Santos Peixoto<sup>4</sup>, Eloïse Gennet<sup>5</sup>, Véronique Andrieu<sup>6</sup>, Aurélie Mahalatchimy<sup>7</sup>

<sup>1</sup> Responsible of Cell therapy/Advanced Therapy Medicinal Products' production at Marseille Public Hospital (AP-HM), Biotherapies Clinical Investigation Center, Marseille, France, <sup>2</sup> Professor of Hematology and Biotherapy, Pharmaceutical Sciences Faculty, C2VN INSERM INRAE 1263 Aix-Marseille University, Director of the cell therapy research centre at Marseille Public Hospital (AP-HM), Marseille, France, <sup>3</sup> Senior Research Fellow in Social Sciences, Centre for Health Law and Emerging Technologies (HeLEX), University of Oxford, Oxford, United Kingdom, <sup>4</sup> Students in 4th year of Pharmaceutical Sciences, Aix-Marseille Université, France, <sup>5</sup> Post-doctoral Researcher in Law, Law Faculty, UMR 7318 International, Comparative and European Law (DICE) CERIC, CNRS, Aix-Marseille University, Toulon University, Pau & Pays de l'Adour University, Aix-en-Provence, France, <sup>6</sup> Senior lecturer in Industrial Pharmacy and Pharmaceutical Regulation, Faculty of Pharmacy, Aix-Marseille University, Research Unit Microbes Evolution Phylogeny and Infection (MEPHI) Aix-Marseille Université, IRD, Marseille, France, <sup>7</sup> Permanent Researcher in law at the French National Centre for Scientific Research (CNRS, chargée de recherche), Law Faculty, UMR 7318 DICE, CERIC, CNRS, Aix-Marseille University, Toulon University, Pau & Pays de l'Adour University, Aix-en-Provence, France.

Acknowledgements: This work has been supported by ANR-funded I-Biolex project (ANR-20-CE26-0067-01, coord. A. Mahalatchimy), M. Morrison is funded by the Leverhulme Trust through grant no RPG-2017-330.

### Introduction

**Background :** Good Manufacturing Practice (GMP) guidelines established by the European Commission are essential to ensure quality, safety and efficacy of medicinal products. Guidelines are designed to address specific risks of medicinal products and as such, are continuously being adapted. Advanced Therapy Medicinal Products (ATMPs) are medicinal products that have been regulated in the European Union from 2007 to cover the emerging field of genes, tissues or cell-based therapies. Dedicated GMP guidelines for ATMPs are enforceable since 2017. Consequently, GMP guidelines covering manufacture of biological active substances and medicinal products for human use including biological active substances (hereafter "Biologicals") have been revised in June 2018 with the objective to prevent overlapping scope.

**Research question and methods:** Our hypothesis is that the biological nature that commonly characterize ATMPs and biologicals may sustain a large body of similarities in the manufacturing aspects as addressed by the respective guidelines. We aim to comparatively analyze the two following texts : *Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products*, and *Manufacture of Biological active substances and Medicinal Products for human use* including biological active substances. Focus has been given on manufacturing, i.e. production recommendations including personnel, premises, equipment, documentation, starting and raw materials, seed lot and cell bank systems. In a systematic approach we highlighted similarities and specificities in the text outlines (paragraph and section titles). Then content has been comparatively investigated based on chosen relevant key words found in both texts (production, operation principles, production area, facilities, cross contamination in production, environmental monitoring and specifications, starting and raw materials).

### Results

#### COMMON TOPICS

##### Premises & Equipments

- Constructed to avoid **cross-contamination**
- **Designed in logical order** to avoid risk
- **Campaigned manufacturing** (separation in place and/or in time)
- **Controlled** for particulate and microbiological contamination, maintained (air vent filters, positive pressure) and validated frequently by effective control strategy
- **Cleaned**
- Effective aseptic operations during the process for biological materials that cannot be sterilized

##### General Documentation

- Documentation for all manufacturing process & method
- Exhaustive **traceability** specially for batch, for starting and raw materials and for all products in contact with cells or tissues
- Traceability records to be for retained for **30 years**

##### Operations / Operating Principles

- Process design **robustness**, minimising variability, enhancing **reproducibility** to ensure quality and safety of the product
- Definition of **critical operational parameters**, **critical operations**
- **Product quality reviews** required
- Rules for process (entries, disinfected, wasted)

##### Starting and raw materials

- Compliance with existing legislation on quality, safety, and traceability of human tissues and cells, especially on donation, procurement and testing

##### Seed lot and cell bank system

- Establishment of seed lots, and cell banks (master and working generation)
- Definition of appropriate specifications and qualification
- Management of a Controlled storage to avoid risk mix up

##### Risk-based approach/Quality risk management

- Prevent and anticipate hazards, control it and apply measures to minimise it
- Based on scientific knowledge and experience
- Quality and safety ensured since the first steps, even for investigational ATMPs.

##### Qualified person and Batch Release/Certification

- Functions of the Qualified Person:
  - Verification and certification of the batches according to manufacturing/marketing/clinical trial authorization
  - Release/certification must be registered and notified if there is a deviation...

##### Personnel

- Qualified
- Trained and retrained

#### SPECIFIC TOPICS

##### Specific Guidelines for ATMPs

##### Aseptic Process & Environmental Monitoring

##### General principles

- Manufacturing to be conducted aseptically to limit introduction of contaminants and cross contamination
- Specific aseptic measures detailed for specific kind of manufacturing processes and open or closed operating systems

##### Aseptic processing validation

- Simulated by media fill test /media process test
- Documented as well as the cleaning process
- Environmental monitoring programme to be applied

##### Specific Guidelines for Biologicals

##### Animal sources

- The manufacturer must follow the Transmissible Spongiform Encephalopathy guidelines and have a recorded health program for other agents. Sick animals must be investigated, and everything has to be documented.
  - Housing must be separated from production and control areas.
- For each animal species, key criteria have to be defined and recorded. In the case of transgenic animals, traceability must be maintained in their creation.

### Discussion and Conclusion

The ATMPs guidelines is a very detailed text covering the investigational and authorized stages from the raw materials to the final product. Technical measures are very extensively introduced for guidance of manufacturers. By contrast, guidelines on Biologicals is briefer and include more general requests and standards ensuring the quality of the product. A large part of manufacturing recommendations are commonly present in the two texts and in line with the manipulation of raw and starting materials of biological origin that raise common challenges in terms of quality reproducibility, traceability and risk of cross or exogenous contaminations. Main specificities associated to the manufacturing of these two categories of medicinal products, are related to specific aspects addressing the control of contamination risk. Regarding ATMPs guidelines, a section is dedicated to aseptic measures covering the entire process management. This specificity is justified by the usual lack of terminal sterilization of the product that requires to adopt preventive strategies to limit the introduction of contaminants. Regarding biologicals, specificities address the challenges of using animal sources in the manufacturing process and the associated risk of contamination. These specificities are relevant because a large proportion of biological medicinal products or active substances are issued from living or post-mortem animal sources, while ATMPs are mostly designed based on human materials. Raw materials of animal origin are poorly addressed in the ATMPs guidelines although this aspect could be of relevance.

#### References

- European Commission, Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products, 22 May 2018.
- European Commission, Manufacture of Biological active substances and Medicinal Products for Human Use, 26 June 2018.

## Quality Control and Batch Release Aspects of Advanced Therapy Medicinal Products

**J. VERAN, M. MORRISON, F. SABATIER, L. CHEY, F. MBODJ, E. GENNET, V. ANDRIEU, A. MAHALATCHIMY**, Quality Control and Batch Release Aspects of Advanced Therapy Medicinal Products, Annual Conference of the European Association of Health Law, Ghent, Belgium, 20-22 April 2022 (POSTER available at <https://shs.hal.science/halshs-03780272v1>)

### Abstract

Quality control and batch release raise specific challenges for ensuring quality and complying with regulatory requirements in order to obtain manufacturing and marketing authorizations for Advanced Therapy Medicinal Products (ATMPs). ATMPs are medicinal products based on genes, cells and tissues that have been specifically regulated in the European Union (EU) from 2007. In the guidelines on Good Manufacturing Practices (GMP) specific to ATMPs from the European Commission, specific requirements cover quality control and batch release. They are distinct from the ones than can be found in other guidelines on GMP applicable to other kinds of biological medicinal products. Through a comparative textual analysis of the GMP guidelines for biological medicinal products and ATMPs, this poster will highlight the key areas of similarities and differences. Our analysis mainly focuses on qualification and validation procedures, batch release process, quality defects and product recalls, and automated production of ATMPs. This analysis reveals why we have two different texts and whether they are based on substantial differences regarding quality control and batch release between ATMPs and other types of biological medicinal products.

# QUALITY CONTROL AND BATCH RELEASE ASPECTS OF ADVANCED THERAPY MEDICINAL PRODUCTS

Julie VERAN<sup>1</sup>, Michael MORRISON<sup>2</sup>, Florence SABATIER<sup>3</sup>, Lea CHEY<sup>4</sup>, Fatou MBODJ<sup>4</sup>, Eloïse GENNET<sup>5</sup>, Véronique ANDRIEU<sup>6</sup>, Aurélie MAHALATCHIMY<sup>7</sup>

<sup>1</sup> Responsible of Cell therapy/Advanced Therapy Medicinal Products' productions at Marseille Public Hospital (AP-HM), Biotherapies Clinical Investigation Center, France; <sup>2</sup> Senior Research Fellow in Social Sciences, Centre for Health Law and Emerging Technologies (HLET), University of Oxford, United Kingdom; <sup>3</sup> Professor of Hematology and Biotherapy, Pharmaceutical Sciences Faculty, C2M-INSERM IIRAE 1263 Aix Marseille University, Director of the cell therapy research centre at Marseille Public Hospital (AP-HM), France; <sup>4</sup> Students in 4<sup>th</sup> year of Pharmaceutical Sciences, Aix Marseille University, France; <sup>5</sup> Post-doctoral Researcher in Law, Law Faculty, UMR 7318 International, Comparative and European Law (ICE) CERIC, CNRS Aix-Marseille University, Buzon University, Paul & Paule Odobour University, Aix-en-Provence, France; <sup>6</sup> Senior lecturer in Industrial Pharmacy and Pharmaceutical Regulation, Faculty of Pharmacy, Aix Marseille University, Research Unit Microbes Evolution Physiology and Infection (MEPI) Aix-Marseille University, IMI, France; <sup>7</sup> Permanent Researcher in law at the French National Centre for Scientific Research (CNRS, CR), Law Faculty, UMR 7318 ICE CERIC, CNRS, Aix Marseille University, Toulouse University, Pau & Pays de l'Adour University, Avenir-Provence, France.

Acknowledgments: This work has been supported by ANR-funded I-Biolex project (ANR-20-CE28-0007-01, coord. A. Mahalatchimy), M. Morrison is funded by the Leverhulme Trust through grant no RPO-2017-330.

## INTRODUCTION

**Background:** Biological medicinal products are products with an active substance produced or extracted from a biological source. Advanced Therapy Medicinal Products (ATMPs) are medicinal products based on genes, cells or bioengineered tissues that have been regulated in the European Union from 2007. Dedicated Good Manufacturing Practice (GMP) guidelines have been established from the European Commission in order to guarantee their quality, efficacy and safety from the development to the marketing authorisation. Consequently, GMP guidelines covering manufacture of *biological active substances* and *medicinal products for human use including biological active substances* (hereafter "biologicals") have been revised in June 2018 to prevent overlapping scope. The manufacturing of biologicals and ATMPs has to comply with guidelines that are established by the European Commission.

**Research question:** We hypothesized that due to biological nature of ATMPs, similarities in part of these guidelines related to quality control and batch release aspects could be evidenced in the texts. This analysis will help to understand why two different texts have been elaborated by analyzing whether they are actually based on specific considerations in terms of quality control and batch release arising from the nature of the products and the processes differences between ATMPs and other biological medicinal products.

**Methods:** We conducted a comparative analysis of the two following regulatory texts: *Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products (focus on from chap. 10 QUALIFICATION to the end) and Manufacture of Biological active substances and Medicinal Products for Human Use*. In a first systematic approach, we identified the similarities and the specificities of texts outline (paragraph and section titles). Then, we analysed contents based on chosen relevant key words that may be diversely used in two texts (control, quality control, strategy of control, certification, release, in process control, quality risk management, analytical techniques/methods, testing etc) in order to highlight similarities and specificities in all aspects related to quality control and batch release.

## RESULTS

### SIMILAR REQUIREMENTS

#### Starting and raw materials

- Compliance with legislations on quality, safety and traceability of human tissues/cells, blood/blood components, and genetically modified cells, (donation, procurement and testing)
- Appropriate level of control and requirements
- Possibility to process starting materials before the results of their testing, but release of finished product conditioned by satisfactory results.

#### Premises and equipment for quality control

- Apart from production.
- Prevention of mix-ups and cross-contamination during testing.
- Storage space (samples and records)

#### Primary containment

- Safe & respect products' characteristics.
- Maintaining quality and prevent spillage.
- Compatibility of labels with ultra-low storage temperatures

#### Batch certification, release

- Initial and final certification based on:
  - Environmental & analytical testing
  - Defined specifications (market authorization, clinical trial authorization)
- By qualified person
- Management of "out of specifications"

#### Documentation

- Specifications, instructions, records/reports.
- On the source, origin, distribution chain, methods and controls.
- Traceability records (30 years).

#### Seed lot and cell bank system

- To prevent drift of properties during handling and storage:
  - Appropriate specifications (number of generations...)
  - Risk of adventitious agents and cross contamination

#### Retained samples for QC retesting

- "Look-back procedure" attesting for the continued suitability of the biological active substance.
- Re-testing of retained samples from previous collection → "last negative donation"

#### In-process control

- Ensures quality consistency
- Happens at appropriate stages of productions

#### Considerations for microbiological risk

- Level of bioburden or need to be sterile defined in MA and CTA for substances and materials at various stages
- Sterilization process allowing to preserve the activity of materials and excipients
- Aseptic process and strategies minimizing the risk of contaminants introduction (quality of starting materials, adapted environmental monitoring, use of closed system, cleaning, use of antimicrobials or antibiotics without interference)

#### Hazard identification/quality risk approach to minimise variability of biological processes and materials and to reduce/control contaminations.

- Subjects are animals, biological agents, premises, equipment and control operations

#### Legend

- Existing or combined sections of each text
- Disseminated requirements within each text

### SPECIFICITIES

#### Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products (2017)

##### Validation of analytical methods

- Suitability for the intended purpose
  - Stability
  - Safety attributes
  - Critical quality attributes
  - Release criteria
  - Stability testing

##### Additional in vitro assays

- potency testing (or proliferation assays...)
- After batch release as supporting data for process validation
  - Cell stocks
  - Obtained from a limited number of passages,
  - Do not cover the entire life cycle of the product
  - Control and release conditions in accordance with principles of cell banks

##### On-going stability program

- For finished products with shorter shelf-life
- After the marketing authorisation
- Stability of specifications during the shelf-life

#### Novel aspects justified by specific challenges of cell-based therapy

- Complexity of products & processes + limited batch sizes + variability of the starting materials (especially in autologous setting) → Flexibility and "Risk-based approach" for appropriate measures of quality control
- At the authorized and investigational stages, from the raw material to the final production

#### Guidelines on the Manufacturing of Biological active substances and Medicinal Products for Human Use (2018)

##### Quality of starting materials or non human origin

##### Animal sources

- 2 types of sources:
  - Live groups (monkeys, horses, sheep, goats, hamsters, cattle...)
  - Animal materials derived post-mortem
- To comply with TSE regulations: suitability of sources/donors, traceability identification system to control all hazards.

##### Strictly controlled selection of donor animals.

- Healthy
- Specific pathogen free (SPF)
- Raised in SPF conditions
- Bred in captivity specifically designed for the purpose of the research

##### Controls & Testing using animals

- Animals used in quality control assays
  - Generic assays, e.g., pyrogenicity,
  - Specific potency assays

#### Quality controls and certification aspects: measures emphasizing procurement and quality of starting materials of animal origin, mitigation of a higher risk of low purity and microbiological contamination, and of greater variability of biological analytical techniques → "risk quality management principles" for appropriate measures of quality control

- Focus on the process, from raw material (principally extracted from animals or donors) to the active substance

## DISCUSSION/CONCLUSION

### Similar spirit of the two texts

- Based on the crucial role of manufacturing and control processes in determining the quality of such types of medicinal products
- To ensure measures related to the biological origin and the related inherent variability of such medicinal products are adopted regarding the requested standards of quality, a major determinant of safety and efficacy for the patients

→ Large set of similarities in their content on quality control and batch release, based on their common biological nature and related risks in terms of quality of starting human and raw materials, traceability, sustainability of quality, compatibility of containments, importance of process controls, strategy for initial and final certification and batch release.

### Explicit Rationale for differences in the two texts

- Substantial specificities due to specific risks, as presented in the scopes and general principles of the texts
- Very detailed text of 90 pages for ATMPs dated of 22/11/2017, and briefer text of 25 pages for biologicals dated of 26/06/2018 that has been revised in order to take into account the new guidelines on ATMPs.

→ Exclusive Guidelines: it is explicitly stated that the text on biologicals do not apply to ATMPs which are covered by specific guidelines.

### Questioning the relevance of having two distinct and exclusive texts

- As ATMPs are a specific category of biologicals, the levels of similarities and differences regarding quality control and batch release is variable, e.g., The "risk-based approach" for ATMPs seems matched to the "risk quality management principles" for biologicals, but the former is more prospective with the idea to anticipate and control current poorly known risks.
- Some specific requirements solely expressed in the ATMPs guidelines may be relevant to other biologicals, e.g., the validation of biological methods used for quality control and testing.

- Some specific requirements solely expressed in the text on Biologicals may be relevant to ATMPs: Because ATMPs could also in the future be designed based on xenogeneic cells and are prone to necessitate the use of raw materials of animal origin (such as cell culture or extraction reagents etc...), it can be anticipated that details of recommendations on animal sources warrant further considerations in ATMP guidelines as it is currently for biologicals.
- The rationale for some style/form differences is unclear: The vocabulary used in the two texts is very different while they have been adopted with a 7 months interval only, and it often refers to the same ideas.

The two texts are presented as exclusive, but they share common aspects.

They share common aspects related to the biological nature of the product. They could benefit from being formulated in a more similar manner to facilitate full understanding and implementation by stakeholders, especially manufacturers.

## REFERENCES

- European Commission, Good Manufacturing Practice specific to Advanced Therapy Medicinal Products, 22 May 2018.
- European Commission, Manufacture of Biological active substances and Medicinal Products for Human Use, 26 June 2018.
- Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, OJ L102, 7.4.2004, p. 48-55 (and following complementary Directives).
- Directive 2001/38/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC, OJ L 31, 8.2.2003, p. 30-40.
- Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms (Recoast) (Text with EEA relevance), OJ L 125, 21.5.2009, p. 75-91.
- Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/269/EEC - Commission Declaration, OJ L 106, 17.4.2001, p. 1-39.

## What are the quality challenges regarding comparability considerations of advanced therapy medicinal products?

V. ANDRIEU, E. GENNET, J. VÉLAN, M. MORRISON, F. SABATIER, A. MAHALATCHIMY, What are the quality challenges regarding comparability considerations of advanced therapy medicinal products? Annual Conference of the European Association of Health Law, Ghent, Belgium, 20-22 April 2022 (POSTER available at <https://archivesic.ccsd.cnrs.fr/AO-DROIT/halshs-03780293v1>)

### Abstract

The question of comparability for Advanced Therapy Medicinal Products (ATMPs) is very often asked during Scientific Advice Meetings at the European Medicines Agency. Indeed, changes to ATMPs manufacturing processes, improvements/changes in equipment, raw materials and critical starting materials, or process scale are frequent in the early stages of development or even after marketing authorization. Quality comparability is the first step in the review of variations procedures of a medicinal product. Indeed, quality information is of major importance with analytical testing, risk-based approach and manufacturing evaluation as it will allow to conclude if non clinical and clinical data on comparability are also needed or not. The text of December 2019 of the Committee for Advanced Therapies (CAT), entitled "Questions and answers, Comparability considerations for Advanced Therapy Medicinal Products" contains the major questions companies can have when a comparison is needed between the pre- and post-change of the manufacturing process of ATMPs. The answers are based on analytical and statistical tools which are needed in frequent experimental changes situations. Generally, this text addresses the issues linked to the demonstration of comparability regarding the quality aspects of ATMPs. Another important text is the ICH Q5E guideline that addresses comparability of biological/biotechnological medicinal products which legally cover ATMPs. However, ATMPs are outside the scope of this guideline, except for the general principles that can be applied to ATMPs. Through of comparative textual analysis of these two texts, this poster will show the complementarity of the information provided, but also the very dynamic impact of the Q&A text targeted on ATMPs in comparison with the large recommendations of the ICH guideline on biotech products.

# What are the quality challenges regarding comparability considerations of advanced therapy medicinal products?

Véronique Andrieu<sup>1</sup>, Eloïse Gennet<sup>2</sup>, Julie Véran<sup>3</sup>, Michael Morrison<sup>4</sup>, Florence Sabatier<sup>5</sup>, Aurélie Mahalatchimy<sup>6</sup>

<sup>1</sup> Senior lecturer in Industrial Pharmacy and Pharmaceutical Regulation, Faculty of Pharmacy, Aix-Marseille University, Research Unit Microbes: Evolution, Phylogeny and Infection (MEPI) Aix-Marseille University (IR), France; <sup>2</sup> Post-doctoral Researcher in Law, Law Faculty, UMR 7118 International Comparative and European Law (DICE) CERIC, CNRS, Aix-Marseille University, Toulouse University, Pau & Pays de l'Adour University, Aix-en-Provence, France; <sup>3</sup> Responsible of Cell therapy/Advanced Therapy Medicinal Products production at Marseille Public Hospital (AP-HM), Biotherapies Clinical Investigation Center, France; <sup>4</sup> Senior Research Fellow in Social Sciences, Centre for Health Law and Emerging Technologies (HLET), University of Galway, United Kingdom; <sup>5</sup> Professor of hematology and biotechnology, Pharmaceutical Sciences Faculty, C2iM-PDREM PNR16 1203 Aix-Marseille University, Director of the cell therapy research centre at Marseille Public Hospital (AP-HM), France; <sup>6</sup> Permanent Researcher in Law at the French National Centre for Scientific Research (CNRS, CR), Law Faculty, UMR 7118 DICE CERIC, CNRS, Aix-Marseille University, Toulouse University, Pau & Pays de l'Adour University, Aix-en-Provence, France.

Acknowledgements: This work has been supported by ANR-funded I-Biolex project (ANR-20-CE26-0007-01, coord. A. Mahalatchimy), M. Morrison is funded by the Leverhulme Trust through grant no RJC-2017-330.

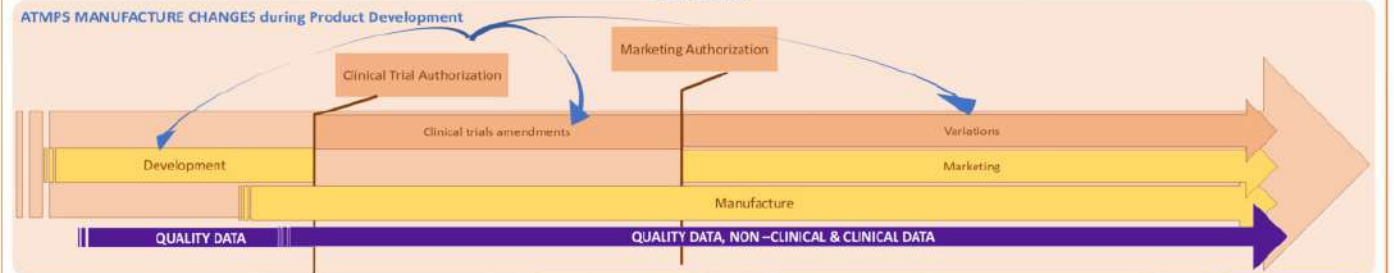
## INTRODUCTION

The question of comparability for Advanced Therapy Medicinal Products (ATMPs) is very often asked during Scientific Advice Meetings at the European Medicines Agency. Indeed, changes to ATMPs manufacturing processes, improvements/changes in equipment, raw materials and critical starting materials, or process scale are frequent in the early stages of development or even after marketing authorization. Quality comparability is the first step in the review of variations procedures of a medicinal product. Indeed, quality information is of major importance with analytical testing, risk-based approach and manufacturing evaluation as it will allow to conclude if non-clinical and clinical data on comparability are also needed or not.

The text of December 2019 of the Committee for Advanced Therapies (CAT), entitled "Questions and answers, Comparability considerations for Advanced Therapy Medicinal Products" contains the major questions companies can have when a comparison is needed between the pre- and post-change of the manufacturing process of ATMPs. The answers are based on analytical and statistical tools which are needed in frequent experimental changes situations. Generally, this text addresses the issues linked to the demonstration of comparability regarding the quality aspects of ATMPs. Another important text is the ICH Q5E guideline that addresses comparability of biological/biotechnological medicinal products. However, ATMPs are outside the scope of this guideline, except for the general principles that can be applied to ATMPs.

Through of comparative textual analysis of these two texts, this poster will show the complementarity of the information provided, but also the very dynamic impact of the Q&A text targeted on ATMPs in comparison with the large recommendations of the ICH guideline on biotech products.

## RESULTS



<p>Assessing the comparability before/after changes should start with comparison of quality data. Changes can happen during the development phase or after marketing authorization.</p>	<p>1/ Comparison of quality attributes with analytical testing, based on active substance &amp; finished product properties;</p>	<p><b>Scope</b> Q&amp;A text: ATMPs, especially cell-based medicinal products ICHQ5E guideline: proteins, polypeptides, and derivatives, and is recommended for vector-based gene therapy medicinal products.</p>	<p><b>Characterization</b> By appropriate techniques (described in ICH Q6B) includes determination of physicochemical properties, biological activity, immunochemical properties (if any), purity, impurities, contaminants, and quantity; each "criteria should be considered as a key point in the conduct of the comparability exercise".  ICHQ5E guideline: analytical tests "chosen to define drug substance/drug product specifications alone" and used at release of the product are generally not "considered adequate" to evaluate comparability, &amp; "Modification, elimination, or addition of a test (i.e., in the specification) might be indicated".  Q&amp;A text: "analytical methods used for release testing are the starting point"; "if the used analytical methods differ, it will be difficult to establish a link between the pre- and post-change material" (Q6).</p>	<p><b>Stability Studies</b> ICHQ5E guideline: "Real-time/real temperature stability studies on the product potentially affected by the change" should be initiated for proteins.  Q&amp;A text: full real time stability studies not required to support comparability for stable ATMPs; in-use stability study is only proposed.</p>
	<p>2/ If not satisfactory, comparison of non-clinical &amp; clinical data. For quality data, comparison integrates all data collected, e.g., routine batch analyses, in-process control, process validation data, characterization or stability.</p>	<p><b>Types of data</b> It is mainly in ICH Q5E that confirmatory nonclinical or clinical studies are appropriate, after comparison of quality data.</p>		



"comparability exercise" based on the physico-chemical and biological properties of the product. Analytical methods for release testing can be used; validated methods not necessary. Even if products are different, comparison method before/after change (in the manufacturing process) is the same.

"A comparability exercise should not only cover evaluation of equivalency of manufactured products but should include also comparison of processes themselves", if relevant.

Knowledge of the manufacture and development data are key words for both texts.

## SPECIFIC TOPICS

The following subjects are only treated in the Q&A text because they are connected to ATMPs.

**Methodology of the comparability exercise:**

- Two main approaches are possible for comparability study of ATMPs: "Side-by-side testing of products in the same analytical run", and "Comparison of post-change data to historical data obtained from pre-change process", the latest one is not recommended (Q7).
- "Statistics may provide useful information to support comparability". "Solely meeting specifications is not considered sufficient to conclude on comparability" (Q11).

**Cell-based products:** the comparability exercise can be conducted with healthy donor materials with justification (Q8).

**When a manufacturing site is added for a marketed product,** "a high degree of comparability is expected" with "comparability assessment of the manufacturing process", "equivalence of the analytical methods" and "comparability of the product itself" (Q12).

**A "comparability exercise" is needed for "critical changes" in the manufacturing of starting materials for ATMPs having an impact on the manufacturing process of the finished product" (Q13).**

**Regulatory consideration:** a change in the manufacturing process results in a variation procedure of the marketing authorization or an amendment of the clinical trial authorization

**Risk-based approach** should be used to determine an appropriate amount of comparability data and to select a suitable set of relevant critical quality attributes (CQAs).

## DISCUSSION/CONCLUSION

<p>The Q&amp;A is limited to ATMPs whereas the guideline is for Biotechnological/Biological Products. ICHQ5E coming into operation in 2005 is used as a Reference text for Q&amp;A of 2019. Nevertheless, only the general principles of ICHQ5E can be applied to ATMPs which are considered to be out of the scope of ICHQ5E due to their characteristics.</p>	<p>The comparability considerations of the ATMPs changes are based on Quality data in the Q&amp;A with a lot of work during the Pharmaceutical Development with the use of modern quality tools; the comparability considerations of the Biotechnological/Biological Products changes are based on quality, non-clinical and clinical data.</p>
<p>The Q&amp;A addresses a number of questions that have been brought to the attention of the EMA by marketing-authorisation holders (MAHs) or European Economic Area competent authorities, on matters related to the quality of medicines. It provides a harmonised position on issues which require clarification, typically during assessment procedures. The Q&amp;A should be read in conjunction with other guidelines.</p>	<p>The obligations to assess changes based essentially on in vitro studies, as in the Q&amp;A, are extremely important for MAHs, because they thus limit in vivo studies on animals or on patients, which are long, expensive and not necessarily ethical.</p>

## Production of ATMPs: What are the specificities for quality aspects?

**A. MAHALATCHIMY, E. GENNET, M. MORRISON, V. ANDRIEU, J. VÉRAN, F. SABATIER**, Production of ATMPs: What are the specificities for quality aspects?, European Society for Gene & Cell Therapy Congress 2022, Edinburgh, the UK, 11-14 October 2022, (POSTER available at <https://shs.hal.science/halshs-03901462>);

Abstract published in Human Gene Therapy, Volume: 33 Issue 23-24: December 14, 2022, A1-A212. <http://doi.org/10.1089/hum.2022.29225.abstracts>

### Abstract

Advanced Therapy Medicinal Products (ATMPs) is a European classification of medicinal products based on genes, cells and tissues that have been specifically regulated in the European Union (EU) from 2007. Their manufacturing (i.e. their production) raises specific challenges for ensuring quality and complying with regulatory requirements in order to obtain manufacturing and marketing authorizations. For this reason, detailed guidelines on Good Manufacturing Practices specific to ATMPs have been adopted by the European Commission, and have been enforceable since 2017. They are distinct from other guidelines on GMP applicable to other kinds of biological medicinal products. Separate GMP guidelines, covering manufacture of biological active substances and medicinal products for human use including biological active substances were revised in June 2018 with the objective of preventing overlaps in scope with the ATMP GMP guidelines. Our hypothesis is that the biological nature that commonly characterizes ATMPs and biologicals may give rise to significant similarities in the manufacturing aspects as addressed by the respective guidelines. Through a comparative textual analysis of the GMP guidelines for biological medicinal products and ATMPs, this poster will highlight the key areas of similarities and differences. This analysis reveals why we have two different texts and whether they are based on substantial differences regarding production between ATMPs and other types of biological medicinal products

# Production of ATMPs: What are the specificities for quality aspects?

Aurélien Mahalatchimy<sup>1</sup>, Eloïse Gennet<sup>2</sup>, Michael Morrison<sup>3</sup>, Véronique Andrieu<sup>4</sup>, Julie Véran<sup>5</sup>, Florence Sabatier<sup>6</sup>

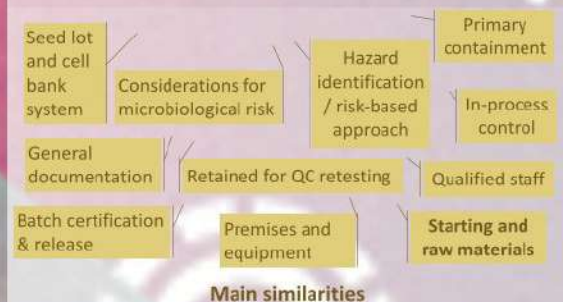
<sup>1</sup> Permanent Researcher in law at the French National Centre for Scientific Research (CNRS, CR), Law Faculty, UMR 7318 DICE CERIC, CNRS, Aix-Marseille University, Toulon University, Aix-en-Provence, France; <sup>2</sup> Post-doctoral Researcher in Law, Law Faculty, UMR 7318 International, Comparative and European laws (DICE) CERIC, CNRS, Aix-Marseille University, Toulon University, Aix-en-Provence, France; <sup>3</sup> Senior Research Fellow in Social Sciences, Centre for Health Law and Emerging Technologies (HeLEX), University of Oxford, United Kingdom; <sup>4</sup> Senior Lecturer in Industrial Pharmacy and Pharmaceutical Regulation, Faculty of Pharmacy, Aix-Marseille University, Research Unit Microbes Evolution Phylogeny and Infection (MEPHI) Aix-Marseille University, IRD, France; <sup>5</sup> Responsible of Cell therapy/Advanced Therapy Medicinal Products' production at Marseille Public Hospital (AP-HM), Biotherapies Clinical Investigation Center, France; <sup>6</sup> Professor of Hematology and Biotherapy, Pharmaceutical Sciences Faculty, C2VN INSERM INRAE 1263 Aix Marseille University, Director of the cell therapy research centre at Marseille Public Hospital (AP-HM), France. **Acknowledgements:** This work has been supported by ANR-funded I-BioLex project (ANR-20-CE16-0007-01, coord. A. Mahalatchimy). M. Morrison is funded by the Leverhulme Trust through grant no RPG-2017-330.

## INTRODUCTION

Advanced Therapy Medicinal Products (ATMPs) is a European classification of medicinal products based on genes, cells and tissues that have been specifically regulated in the European Union (EU) from 2007. Their manufacturing (i.e. their production) raises specific challenges for ensuring quality and complying with regulatory requirements in order to obtain manufacturing and marketing authorizations. Hence, on top of its **guideline on the manufacturing of Biological active substances and Medicinal Products for Human Use** (26 June 2018, 25 pages revised to consider the new ATMP guidelines), the European Commission also issued **Good Manufacturing Practice specific to Advanced Therapy Medicinal Products** (22 November 2017, very detailed text of 90 pages).

Our hypothesis is that the biological nature that commonly characterizes ATMPs and biologicals may give rise to significant similarities in the manufacturing aspects as addressed by the respective guidelines. Through a comparative textual analysis of the GMP guidelines for biological medicinal products and ATMPs, this poster will highlight the key areas of similarities and differences. This analysis reveals why we have two different texts and whether they are based on substantial differences regarding production between ATMPs and other types of biological medicinal products.

## COMMON TOPICS



### Main similarities

- Manipulation of raw and starting materials of biological origin raising common risks and challenges of quality reproducibility and sustainability, traceability and risk of cross or exogenous contaminations (compatibility of containments, importance of process controls, strategy for initial and final certification and batch release)**
- Similar spirit of the two texts**
  - Crucial role of manufacturing and control processes in determining the quality
  - Biological origin and related inherent variability → requested standards of quality

## SPECIFICITIES OF BIOLOGICALS VERSUS ATMPs

	ATMPs	BIOLOGICALS
Specific risks	as presented in the scopes and general principles of each text	
Specificities for manufacturing		
Stages to be considered	from raw material to final production	from raw material to active substance
Appropriate measures of quality control	<b>Complexity of products &amp; processes, limited batch series, variability of starting materials</b> (especially in autologous setting) > Flexibility and "Risk-based approach"	<b>Procurement and quality of starting materials of animal origin, mitigation of a higher risk of low purity and microbiological contamination, and of greater variability of biological analytical techniques</b> > "risk quality management principles"
Especially control of contamination on risk	Section dedicated to <b>aseptic measures</b> covering the entire process management. <i>Rationale:</i> Usual lack of terminal sterilization of the product requiring preventive strategies to limit the introduction of contaminants.	Provisions addressing the use of <b>animal sources</b> in the manufacturing process and associated contamination risk. <i>Rationale:</i> A large proportion of biologicals or active substances are issued from living or post-mortem animal sources versus ATMPs mostly designed based on human materials.

## DISCUSSION & CONCLUSION

Explicitly stated that the text on biologicals does not apply to ATMPs which are covered by specific guidelines, but the two texts share common aspects related to the biological nature of the product:  
**Relevance of having two distinct and exclusive texts?**

**Some ATMPs specific requirements may be relevant to other biologicals**

e.g., the validation of biological methods used for quality control and testing.

**Variable levels of similarities and differences**

As ATMPs are a specific category of biologicals, e.g., the "risk-based approach" for ATMPs seems matched to the "risk quality management principles" for biologicals, but the former is more prospective with the idea to anticipate and control current poorly known risks.

**Some specific Biologicals requirements may be relevant to ATMPs**

e.g., Raw materials of animal origin are poorly addressed in the ATMPs guidelines although ATMPs could also in the future be designed based on xenogeneic cells and are prone to necessitate the use of raw materials of animal origin (such as cell culture or extraction reagents etc..).

**Unclear rationale for some style/form differences**

Very different vocabulary used in the two texts while they have been adopted with a 7 months interval only, and often refer to the same ideas.

**The two texts could benefit from being formulated in a more similar manner to facilitate full understanding and implementation by stakeholders, especially manufacturers.**

## The challenges of Advanced Therapy Medicinal Products manufacturing in the European Union: Strengths and limits of current regulatory tools

**L.-S. GILBERT, A. DELAGE, H.-Y. KUO, A. COUTURIER, A. MAHALATCHIMY,** The challenges of Advanced Therapy Medicinal Products manufacturing in the European Union: Strengths and limits of current regulatory tools, European Society for Gene & Cell Therapy Congress 2023, Brussels, Belgium, 24-27 October 2023 (POSTER available at <https://shs.hal.science/halshs-04290578v1>)

### Abstract

Advanced Therapy Medicinal Products (ATMPs) is a European classification of medicinal products based on genes, cells and tissues specifically regulated in the European Union (EU) from 2007. Any company wishing to manufacture ATMPs in the EU must hold a manufacturing authorisation issued by the national competent authority of the Member State where they carry out these activities. Ensuring the quality of medicines is a criterion to obtain ATMPs' marketing authorisation issued by the European Commission under the "centralised procedure" after a single application to the European Medicines Agency. All ATMPs marketed in the EU must be produced in accordance with EU quality standards to ensure the quality, safety and efficacy of medicines for the patients: Good Manufacturing Practice (GMP) principles and guidelines dedicated to ATMPs enforceable since 2017, and relevant parts of the European Pharmacopoeia provide the main regulatory standards to comply with. The manufacture, meeting the GMP requirements from the raw materials to the final product, is particularly challenging for ATMPs regarding their level of complexity and their specific characteristics, especially the use of substances of human origin as starting materials, and the reproducibility when using live biological samples. The ATMPs' manufacturer has to maintain costly technical specifications capable of guaranteeing the reproducibility of the medicine's composition in accordance with GMP guidelines and the specific requirements of the ATMP marketing authorisation. Regulatory requirements are often seen as obstacles to the development of ATMPs. Nevertheless, they mainly provide a set of solutions to overpass the technical obstacles of ATMPs' manufacturing in order to ensure their quality for the safety of patients. It appears clearly within the various supporting regulatory tools currently available at the European level, which include both guidance documents and procedures for interactions with regulators. This poster will provide an overview of the challenges of ATMPs' manufacturing and link them to the relevant supporting regulatory tools highlighting both their strengths and their limits in the context of ATMPs development for patients.



I-BIOLEX



CERIC

# The challenges of Advanced Therapy Medicinal Products manufacturing in the European Union: strengths and limits of current regulatory tools

Luc-Sylvain Gilbert<sup>1</sup>, Auxane Delage<sup>2</sup>, Dr. Hsin-Yu Kuo<sup>3</sup>, Dr. Anna Couturier<sup>4</sup>, Aurélie Mahalatchimy<sup>5</sup>

EuroGCT Information Officer on Ethical, Legal & Societal Issues (ELSI), Research Engineer in law, Law Faculty, UMR 7318 International, Comparative and European laws (DICE) CERIC, CNRS, Aix Marseille Univ, Toulon Univ, Aix-en-Provence, France; <sup>2</sup>EuroGCT Information Officer on ATMP Product Development Pathway, Centre for Regenerative Medicine, Institute for Regeneration and Repair, University of Edinburgh, UK; <sup>3</sup>EuroGCT Project Manager, Centre for Regenerative Medicine, Institute for Regeneration and Repair, University of Edinburgh, UK; <sup>4</sup>EuroGCT Deputy coordinator and WP4 leader, Permanent Researcher in law at the French National Centre for Scientific Research (CNRS, UK), Law Faculty, UMR 7318 DICE CERIC, CNRS, Aix Marseille Univ, Toulon Univ, Aix-en-Provence, France. **Acknowledgments:** This work has been supported by European Union's Horizon 2020 EuroGCT project (GA No 965241) and by ANR-funded I-Biolex project (ANR-20-CE26-0007-01). Contact: [luc.gilbert@univ-amu.fr](mailto:luc.gilbert@univ-amu.fr)

## Introduction

Advanced Therapy Medicinal Products (ATMPs) is a European classification of medicinal products based on genes, cells & tissues specifically regulated in the European Union (EU) from 2007. All ATMPs marketed in the EU must be produced in accordance with EU quality standards to ensure the quality, safety & efficacy of medicines for the patients: Good Manufacturing Practice (GMP) principles & guidelines dedicated to ATMPs enforceable since 2017, & relevant parts of the European Pharmacopoeia provide the main regulatory standards to comply with. What are the challenges of ATMPs' manufacturing & what regulatory tools address them?

### Challenges of ATMPs manufacturing

**Extreme logistical complexity:** collection of patient cells, transportation to manufacturing facility, & supply of the finished ATMP to the patient's healthcare

**Validation of the consistency of the ATMP production process:** autologous nature & small sample sizes limiting the number of analytical tests

**The use of substances of human origin composed of live cells with a short shelf life from the starting point of procurement of the cellular starting material up to the final product's administration raises complex manufacturing challenges**

**Maintaining sterility** throughout entire manufacturing process

**Degree of variability of the finished product:** biological materials &/or complex manipulation steps, especially in autologous setting

**High production & development costs:**

- need for specialised premises, equipment, skilled personnel, rigorous monitoring & quality control system, linked with a relatively long-term return on investment;
- autologous cell therapies +++: need to scale-out & potential need for manufacturing at point-of-care;
- for smaller companies & academic institutions +++: lack of qualified personnel, infrastructure & capital for moving to late phase studies.

Need for **continuous monitoring & controls**

**Complex manufacturing process & regulatory approval timelines:** potential delays in patients' access to ATMPs

**Demonstration of comparability** between production processes & batches

## Regulatory provisions

- **European Commission (EC) GMP guidelines for ATMPs:** EC adapted the GMP requirements for medicinal products to the specific characteristics of ATMPs & their complex manufacturing to issue mandatory guidelines for ATMPs applicable to all type of settings. The guidelines foster a risk-based approach to manufacture & testing of ATMPs, to design the organisational, technical, & structural measures to provide flexibility & ensure a high 'pharmaceutical quality system' that safeguards ATMP's quality. These requirements include: Risk-based approach / Personnel / Premises / Equipment / Documentation / Starting & raw materials / Seed lot & cell bank system / Production / Qualification & validation / Qualified person & batch release / Quality control / Outsourced activities / Quality defects & product recalls / Environmental control measures for ATMPs containing or consisting of GMOs / Reconstitution of product after batch release / Automated production of ATMPs
- **European Medicines Agency (EMA)**
  - o [Quality flowchart on ATMPs](#) (2021) to help ATMPs developers navigate the most important quality requirements & foster development of ATMPs ensuring quality for the safety of patients;
  - o [Questions & answers on comparability considerations for ATMPs](#), 2019, (EMA/CAT/499821/2019);
  - o [Questions & answers on the principles of GMP for the manufacturing of starting materials of biological origin used to transfer genetic material for the manufacturing of ATMPs](#), 2021, (EMA/246400/2021);
  - o [Guideline on the quality, non-clinical & clinical aspects of gene therapy medicinal products](#), 2018, (EMA/CAT/80183/2014);
  - o [Guideline on quality, non-clinical & clinical requirements for investigational advanced therapy medicinal products in clinical trials](#), 2019, (EMA/CAT/852602/2018)
  - o [Reflection paper on design modifications of gene therapy medicinal products during development](#), 2011, (EMA/CAT/GTWP/44236/2009).
- **Council of Europe European Pharmacopoeia:** quality standards & controls.
- **General principles** of ICH Q5E on 'Comparability of biotechnological/biological products subject to changes in their manufacturing process'.

## Interactions with regulators

**Interactions with EMA:** EMA scientific advice & protocol assistance to manufacturers, published common interpretation of EU GMP, & guidance helping manufacturers to navigate the complex regulatory landscape & optimise their ATMPs development & manufacturing processes.

**Innovation Task Force (ITF)**  
Forum to foster early dialogue with applicants on innovative aspects in medicines development

**Priority Medicines (PRIME)**  
Support for the development of medicines targeting unmet medical need

**Small & medium-sized enterprise (SME) status**  
Regulatory & administrative assistance, & fee incentive for micro & SME

**Interactions with national competent authorities:** any company wishing to manufacture ATMPs in the EU must hold a manufacturing authorisation issued by the national competent authority of the Member State where they carry out these activities.

Provide support & scientific advice to ATMPs manufacturers

Conduct on-site inspections

Are responsible for the official release of the batches by the control authorities

**Maintenance of EudraGMPD database** on manufacturing authorisations, GMP & good distribution practices, whose content is provided by national competent authorities

## Conclusion / Discussion

Notwithstanding the regulatory provisions providing a set of solutions to overpass the technical obstacles of ATMPs' manufacturing, some challenges still to be addressed:

- **Due to ATMPs diversity** (from a simple progenitor cell products up to very complex ATMPs), the scientific guidelines might not always be fully applicable to a given medicinal product under development: case by case approach;
- **To avoid regulatory cost burden & imbalance for ATMPs' developers,** needs to update the European Pharmacopoeia in the gene & cell therapy field & clarify the hierarchy between these requirements & the EU provisions;
- **Multiple sites manufacturing issues involved in scaling-out production of autologous ATMPs:** to ensure the quality of the manufacturing process for each manufacturing site involved, mitigating costly transition to GMP & time-consuming confirmatory clinical qualification studies, the 2023 [Proposal for a Directive reforming the Union code relating to medicinal products for human use](#) contains provisions on decentralised production sites potentially near to the patient. In particular, Article 142 states that by derogation "the manufacturing authorisation shall not be required for [...] the decentralised sites carrying out manufacturing or testing steps under the responsibility of the qualified person of a central site referred to in Article 151(3)";
- **Raw materials of animal origin are poorly addressed in ATMPs guidelines:** ATMPs could also in the future be designed based on xenogeneic cells & are prone to necessitate the use of raw materials of animal origin (cell culture or extraction reagents etc.). It can be anticipated that details of recommendations on animal sources warrant further considerations in ATMP guidelines as it is currently for biologicals.



# **II**

## **Clinical aspects**

## What specificity for the clinical aspects of investigational advanced therapy medicinal products?

**E. GENNET, F. SABATIER, J. VÉRAN, D. A. FATOU, N. MONGALGI, V. ANDRIEU, M. MORRISON, A. MAHALATCHIMY**, What specificity for the clinical aspects of investigational advanced therapy medicinal products?, Annual Conference of the European Association of Health Law, Ghent, Belgium, 20-22 April 2022 (POSTER available at <https://shs.hal.science/halshs-03780286v1>)

### Abstract

While Advanced Therapy Medicinal Products (ATMPs), a European legal classification of medicinal products based on genes, cells and tissues, raise specific quality issues, the latter are particularly acute in the context of clinical trials of ATMPs. In comparison to more traditional medicinal products, ATMPs have been subject to specific regulatory provisions in the European Union (EU) since 2007. In addition, many new guidelines have also been adopted to consider the issues raised by ATMPs. Most importantly for investigational ATMPs, the European Commission has adopted and published Guidelines on Good Clinical Practice specific to ATMPs in 2019. Not only are these guidelines targeting ATMPs, they also have a dedicated section on investigational ATMPs exploring the particular challenges raised when tissues and cells of human origin, are administered to a human trial subject, including when ATMPs incorporate medical devices, or delivered with the aim of reconstituting a given bodily tissue or organ. The aim of this poster is to highlight the specificity of quality requirements of investigational ATMPs by examining the dedicated subsections in the guidelines published by the European Commission and analysing them through the lens of the corresponding scientific literature. On the basis of the identification of the specific requirements regarding the quality of investigational ATMPs, the poster will reveal why they raise specific challenges and why these challenges deserve separate regulation in order to demonstrate quality in clinical trials.

# What specificity for the clinical aspects of investigational advanced therapy medicinal products?

Eloïse Gennet<sup>1</sup>, Florence Sabatier<sup>2</sup>, Julie Véran<sup>3</sup>, Diack Adja Fatou<sup>4</sup>, Nada Mongali<sup>1</sup>, Véronique Andrieu<sup>5</sup>, Michael Morrison<sup>6</sup>, Aurélie Mahalatchimy<sup>7</sup>

<sup>1</sup> Post-doctoral Researcher in Law, Law Faculty, UMR 7318 International, Comparative and European Laws (IDEE) CERIC, CNRS, Aix-Marseille University, Toulon University, Pau & Pays de l'Adour University, Aix-en-Provence, France; <sup>2</sup> Professor of Hematology and Biotherapy, Pharmaceutical Sciences Faculty, C2VN INSERM/UMR 1263 Aix-Marseille University, Director of the cell therapy research centre at Marseille Public Hospital (AP-HM), France; <sup>3</sup> Responsible of Cell therapy/Advanced Therapy Medicinal Products' production at Marseille Public Hospital (AP-HM), Biotherapies Clinical Investigation Center, France; <sup>4</sup> Students in 4<sup>th</sup> year of Pharmaceutical Sciences, Aix-Marseille University, France; <sup>5</sup> Senior lecturer in Industrial Pharmacy and Pharmaceutical Regulation, Faculty of Pharmacy, Aix-Marseille University, Research Unit Microbes Evolution Phylogeny and Infection (MEPIH) Aix-Marseille University, IRE, France; <sup>6</sup> Senior Research Fellow in Social Sciences, Centre for Health Law and Emerging Technologies (iHeLx), University of Oxford, United Kingdom; <sup>7</sup> Permanent Researcher in Law at the French National Centre for Scientific Research (CNRS, CR), Law Faculty, UMR 7313 DICE CERIC, CNRS, Aix-Marseille University, Toulon University, Pau & Pays de l'Adour University, Aix-en-Provence, France.

Acknowledgments: This work has been supported by ANR-funded I-Biolex project (ANR-20-CE25-0007-01, coord. A. Mahalatchimy), M. Morrison is funded by the Leverhulme Trust through grant no RPG-2017-330.

## BACKGROUND AND AIM

While Advanced Therapy Medicinal Products (ATMPs), a European legal classification of medicinal products based on genes, cells and tissues, raise specific quality issues, the latter are particularly acute in the context of clinical trials and thus cannot be treated as any other medicine, notably because of their manufacturing constraints and short shelf-life. In comparison to more traditional medicinal products, ATMPs have been subject to specific regulatory provisions in the European Union (EU) since 2007. In addition, many guidelines have also been adopted to consider the issues raised by ATMPs.

Clinical trials with ATMPs are generally governed by Regulation 536/2014 on clinical trials, which came into effect on 31 January 2014, as well as ICH E6 Guidelines on Good Clinical Practice (GCP). For clinical trials conducted in the EU, it is mandatory to comply with GCP. Most importantly for investigational ATMPs, the European Commission has adopted and published 2019 Guidelines on GCP specific to ATMPs, as required by Article 4 of Regulation (EC) n°1394/2007 on ATMPs. These guidelines are both adapting ICH guidelines to ATMPs characteristics and providing additional measures that have been considered necessary. However, they are not exhaustive as they explain only some specificities of ATMPs and they are complementary to the general rules. Not only are these guidelines targeting ATMPs specifically, they also have a dedicated section on the quality of investigational ATMPs.

The aim of this poster is to highlight the specificity of quality requirements of investigational ATMPs in order to reveal the specific challenges they are addressing and why these challenges deserve separate regulation in order to demonstrate quality in clinical trials.

## METHODOLOGY

The research work has consisted in examining the elements of the 2019 Guidelines from the European Commission that were dedicated to the quality of investigational ATMPs, in order to analyze them through the lens of the corresponding scientific literature.

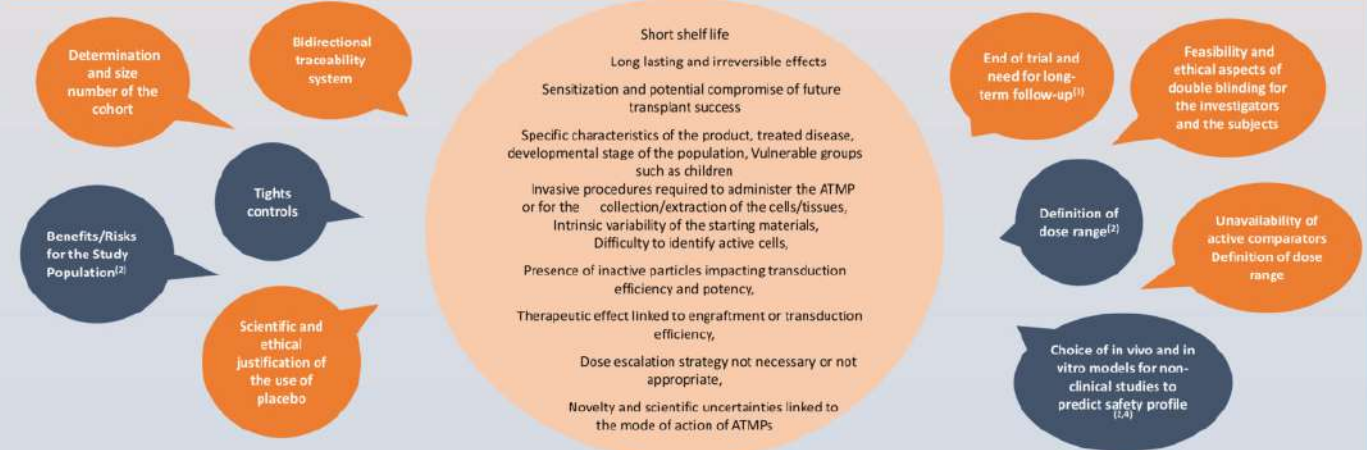
The first stage of the research has consisted in the study of aforementioned guideline through the analysis of the general structure of the guidelines regarding the challenges covered, and a more detailed analysis of the quality aspects, especially regarding the section on the quality of investigational ATMPs. More specifically, the subsections of the guideline that were relevant to the analysis of specific quality requirements for investigational ATMPs were identified. Then, the main issues at stake for each subsection were formulated and organized by topic.

During the second stage of the research, a literature review was conducted in PubMed and Web of Science, using queries such as ("Investigational Advanced Therapy Medicinal Products") or ("Advanced Therapy Medicinal Products" AND "Clinical Trials" [Title]). The research generated 29 results, among which only 4 articles were selected for further content analysis, on the basis of their relevance for the study of specific quality requirements for investigational ATMPs at the EU level of governance.

At the last stage of research, analysis of the literature was compared to the results from the guideline analysis.

## RESULTS

### Main challenges for ATMPs: the design and conduct of clinical trials



### Conclusion

Case by case evaluation of the various aspects of the design of the early-phase ATMPs clinical trials and various levels of documentation to be provided for clinical trials authorisation

### Guidelines' specific requirements concerning the quality of experimental ATMPs

#### General considerations

Compliance with the European Commission Guidelines on Good Manufacturing Practice for Advanced Therapy Medicinal Products

#### Starting materials

- Impact of the variability of donor or patient based starting material to define release specifications for cell-based ATMPs (for autologous products: disease status of the patient)
- Confirmation of compliance with European directives on quality and safety of human tissues and cells, and human blood and blood components for their donation, procurement and testing
- Confirmation of the traceability system's establishment with bidirectional tracking of tissues and cells from donation to administration

#### Storage, transport and handling conditions

- Detailed instructions of the reconstitution process from sponsor to the administration site:
  - o To specify if the reconstitution requires the use of solvents and/or other materials
  - o Reconstitution to be described in the Investigators Brochure or in its Annex
  - o For complex reconstitution process: training to be provided

#### Investigational ATMP Reconstitution before administration

- Detailed conditions from sponsor to investigator (e.g., temperature conditions)
  - o When short-shelf life: timelines to be clearly documented in trial records
  - o For handling process: adequate training of the investigator

#### Medical devices (MD)

- MD integrated within the investigational ATMP (combined ATMP):
  - o Information on the characteristics, performance and intended use of MD, AND
  - o Compliance with the relevant MD general safety and performance requirements (Regulation 2017/745), OR justification of the MD suitability for the intended use on the basis of these requirements
- MD used with investigational ATMP (not integrated):
  - o Cover letter with:
    - List of MD to be investigated in the clinical trial
    - Statement on the existence of CE-marked for the MD intended use.
    - Summary information on characteristics, performance, intended use, and regulatory status of MD

## DISCUSSION AND CONCLUSION

Many different aspects are covered in this guideline. They are **essentials to patients' well-being and product safety**. They permit to **avoid mistakes and minimize risks through the design and the conduct of clinical trials**. As such, they guide medicines' developers in the innovative sector of ATMPs.

ATMPs are innovative and more complicated than traditional or other biological drugs → precise and specific requirements which can raise logistical issues, such as the adaptation needed in terms of equipment and logistics<sup>(2)</sup>.

High risks associated with the manufacturing process and the product → higher expectations for control  
Many sources of variability can influence the quality of the investigational ATMPs → they should all be considered and minimized to avoid distorted results<sup>(3)</sup>

Variability can lead to the discontinuation of the clinical trial although it can also be related to a strategic decision of the sponsor, the poor recruitment of clinical trials' participants or serious adverse events<sup>(5)</sup>

For phase 1 clinical trials, quality and safety strongly overlap.

**Solution to address the challenges of quality in the context of ATMPs clinical trials: to engage in a pre-clinical trials application meeting with regulatory agencies, such ANSM as it is proposed in France<sup>(4)</sup>**

## REFERENCES

- (1) European Commission, Guideline on Good Clinical Practice specific to Advanced Therapy Medicinal Products, 10 October 2019, C(2019) 7140 final.
- (2) Iglesias-Lopez C, Agutti A, Vallano A, Obach M, Methodological characteristics of clinical trials supporting the marketing authorisation of advanced therapies in the European Union. *Front Pharmacol*. 2021 Nov 29; 12:73732. doi: 10.3389/fphar.2021.73732.
- (3) Jones DR, McBlane JW, McNaughton G, Rajakumaraswamy N, Wydenbach K. A regulatory perspective of clinical trial applications for biological products with particular emphasis on Advanced Therapy Medicinal Products (ATMPs). *Br J Clin Pharmacol*. 2013 Aug;76(2):203-9. doi: 10.1111/bcp.12057. PMID: 23216470; PMCID: PMC3731595.
- (4) Lucas-Samuel S, Ferry N, Trouvin JH. Overview of the Regulatory Oversight Implemented by the French Regulatory Authorities for the Clinical Investigation of Gene Therapy and Cell Therapy Products. *Adv Exp Med Biol*. 2015;871:73-85. doi: 10.1007/978-3-319-18618-4\_A. PMID: 26374213.
- (5) Hanna E, Rémusat C, Auquier P, Toumi M. Risk of discontinuation of Advanced Therapy Medicinal Products clinical trials. *J Mark Access Health Policy*. 2016 Aug 24. doi: 10.3402/jmahp.v4.32232. PMID: 27570614; PMCID: PMC4973442.
- (6) European Commission, Guidelines of 22 November 2017 on Good Manufacturing Practice for Advanced Therapy Medicinal Products, C(2017) 7694.
- (7) Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC; OJ L33, 8.2.2003, p. 30-40. CELEX number: 32002L0098
- (8) Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, OJ L 102, 7.4.2004, p. 48-58. CELEX number: 32004L0023

## Specific guidelines requirements for clinical trials with Advanced Therapy Medicinal Products in the European Union

**A. MAHALATCHIMY, E. GENNET, M. MORRISON, V. ANDRIEU, J. VÉRAN, F. SABATIER**, Specific guidelines requirements for clinical trials with Advanced Therapy Medicinal Products in the European Union, European Society for Gene & Cell Therapy Congress 2022, Edinburgh, the UK, 11-14 October 2022 (POSTER available at <https://shs.hal.science/halshs-03901386v1>);

Abstract published in Human Gene Therapy, Volume: 33 Issue 23-24: December 14, 2022, A1-A212. <http://doi.org/10.1089/hum.2022.29225.abstracts>

### Abstract

Advanced Therapy Medicinal Products (ATMPs), a European legal classification of medicinal products based on genes, cells and tissues, raise specific issues in the context of clinical trials. In comparison to more traditional medicinal products, ATMPs have been subject to specific regulatory provisions in the European Union (EU) since Regulation (EC) n1394/2007. Yet for the clinical trials with ATMPs, the general regime laid out in Regulation 536/2014 on clinical trials (which came into effect on 31 January 2022) applies, together with the ICH E6 Guidelines on Good Clinical Practice (GCP). For clinical trials conducted in the EU, compliance with GCP is mandatory. The European Commission has also adopted and published 2019 Guidelines on GCP specific to ATMPs, as required by Article 4 of Regulation (EC) n1394/2007 on ATMPs. These guidelines both adapt the ICH guidelines to ATMPs' characteristics and provide additional measures that have been considered necessary. However, they are not exhaustive as they explain only some specificities of ATMPs and they remain complementary to the general rules. After having analysed these documents, we will highlight the specificity of requirements for investigational ATMPs in order to reveal the specific challenges they are addressing and why these challenges warrant separate regulation in order to obtain clinical trials' authorisation for investigational ATMPs.

# Specific guidelines requirements for clinical trials with Advanced Therapy Medicinal Products in the EU

Aurélie Mahalatchimy<sup>1</sup>, Eloïse Gennet<sup>2</sup>, Michael Morrison<sup>3</sup>, Véronique Andrieu<sup>4</sup>, Julie Véran<sup>5</sup>, Florence Sabatier<sup>6</sup>

<sup>1</sup>Permanent Researcher in law at the French National Centre for Scientific Research (CNRS, CR), Law Faculty, UMR 7318 DICE CERIC, CNRS, Aix-Marseille Univ., Toulon Univ., Aix-en-Provence, France; <sup>2</sup>Post-doctoral Researcher in Law, Law Faculty, UMR 7318 International, Comparative and European laws (DICE) CERIC, CNRS, Aix-Marseille Univ., Toulon Univ., Aix-en-Provence, France; <sup>3</sup>Senior Research Fellow in Social Sciences, Centre for Health Law and Emerging Technologies (HeLEX), Oxford Univ., UK; <sup>4</sup>Senior lecturer in Industrial Pharmacy and Pharmaceutical Regulation, Faculty of Pharmacy, Aix-Marseille Univ., Research Unit Microbes Evolution Phylogeny and Infection (MEPHI) Aix-Marseille Univ., IRD, France; <sup>5</sup>Responsible of Cell therapy/Advanced Therapy Medicinal Products' production at Marseille Public Hospital (AP-HM), Biotherapies Clinical Investigation Center, France; <sup>6</sup>Professor of Hematology and Biotherapy, Pharmaceutical Sciences Faculty, C2VN INSERM INRAe 1263 Aix Marseille Univ., Director of the cell therapy research centre at Marseille Public Hospital (AP-HM), France. **Acknowledgements:** This work has been supported by ANR-funded I-BioLex project (ANR-20-CE26-0007-01, coord. A. Mahalatchimy). M. Morrison is funded by the Leverhulme Trust through grant no RPG-2017-330.

## INTRODUCTION

Advanced Therapy Medicinal Products (ATMPs), a European legal classification of medicinal products based on genes, cells and tissues, raise specific issues in the context of clinical trials (CT). Several normative instruments apply at the European level (see table opposite). The 2019 guidelines from the European Commission on Good Clinical Practice (GCP) both adapt the ICH E6 to ATMPs' characteristics and provide necessary additional measures. However, they are not exhaustive as they explain only some specificities of ATMPs and they remain complementary to the general rules. We will highlight the specific requirements for investigational ATMPs (ATIMPs) to reveal the particular challenges they are addressing and why these challenges warrant separate regulation in order to obtain CT' authorisation for ATIMPs and potentially for further marketing authorisation application (MAA).

Level	Text	General	ATMPs
Legal		Regulation 536/2014 on clinical trials	Regulation 1394/2007 on ATMPs
Regulatory guidelines		ICH E6 on GCP	Specific GCP

### Clinical trials design

- Study population**  
**ATMPs characteristics** > Subjects' risks & benefits, interpretable data
- Cohorts**  
**Limited manufacturing capacity** > Staggered treatment
- Comparators**  
**No active comparator** > Best standard of care, or intra-subject control
- Blinding**  
**Double blinding unethical/ unfeasible** > For subjects' where possible; blinding observers if unblinded investigator
- Placebo**  
**Invasive procedures** > No more than minimal risk/burden for control groups
- Dosing**  
**Identifying active cells; inactive particles with impact; dose variation of cells numbers; complex dosing** > For long-term effects, dose escalation & repeated dosing Or exploratory dose = therapeutic dose
- Trial end**  
**Potential need for long-term follow-up** > Clearly defined event marking trial end

### Monitoring

#### Human origin of cells/tissues >

Traceability requirements/ long-term follow-up arrangements compliance; For ATMPs accountability records kept at CT site, possible requirement of adaptation of study requirements' form, records reflecting ATMPs specificities

### Administration of out of specifications products

#### Variability in ATMPs nature >

Exceptionally to avoid immediate significant hazard, manufacturer/ sponsor to provide risks evaluation; records of request kept in manufacturing site; relevant authority to be notified

## ATMPs Guidelines content and potential challenges targeted

### Non-clinical studies

**Safety: incompatibility between human & animal species** > Case by case assessment of non-clinical data

### Quality

- General considerations**  
**ATMPs characteristics** > Compliance with GMP for ATMPs
- Starting materials**  
**Variability** > Compliance with directives on blood and cells/tissues; Traceability system's with bidirectional tracking
- Storage, transport & handling conditions**  
**e.g., temperature, short-shelf life** > Timelines in trial records; Investigator's training
- Reconstitution before administration**  
**Potentially complex** > use of solvents and/or other materials?; Training
- Medical devices (MD)**  
**Combined ATIMP** > MD characteristics, performance and intended use + MD Regulation Compliance OR justification of MD suitability for intended use  
**MD used with ATIMP** > List of investigated MD; statement on CE-marked MD; MD characteristics, performance, intended use, and regulatory status

### Information in Investigator Brochure and Protocol

**Placebo:** Procedure's risk  
**Dosing:** For complex dosing ATMPs, adequate level of understanding & compliance by investigator and those involved in CT  
**End of trial:** how follow-up activities will be performed after end of trial

**Product information in IB:**  
- product risks;  
- previous/ concomitant (or required further treatments) potential impact;  
- treatment failure risk;  
- emerging issues.  
**Risk minimization measures:** Where appropriate, measures to protect CT subjects from identified risks:

**Quality:** reconstitution before administration: Description of Reconstitution

**Upstream interventions on subjects and administration procedures:** Detailed instructions, possibly in separate document available at site if attached as Annex

**Long-term follow-up general principles & remote follow-up:**  
- Follow-up scheme & after trial follow-up activities;  
- Detailed arrangements for remote conduct of follow-up;  
- How to ensure collected data quality

### CT Safe conduct

- ATIMP Handling**  
**Infectious biological material** > Handling and disposal detailed instructions  
**Bacterial/viral vector with shedding potential** > Risks and precautionary measures for subject and/or caregivers  
**Risks for health care professionals** > Risk minimisation measures
- Risk minimization measures**  
**e.g. No sterility test result at product release; CT subject risk of cytokine release syndrome** > Mitigation measures; Information to Investigator on measures before treatment

### Long-term follow up

- General principles**  
**Safety profile not fully elucidated** > Duration of ATIMP biological activity; long term follow-up scheme; Length of observation period; relevance of other product bibliographic data; not required if low risk of delayed adverse events; monitoring of CT subject follow-up in MAA
- Remote follow-up**  
**e.g. distance from residence** > Gathering data process; Sponsor responsible for adverse events collection robust system; Writing of each party involved responsibilities; Collected data centralisation & availability for inspection at CT site
- Premature end or termination**  
Specificities where CT subjects will and foreseen long-term follow-up
- Patient care alerts**  
For CT subjects depending on ATMPs characteristics to inform treating physicians to facilitate medical care in case of emergency & reporting of adverse events

### Upstream intervention on subjects and administration procedures

- General**  
**In autologous setting, deviation from standard clinical practice** > Subject's risks + impact on product quality and safety;  
**Procedure complexity and novelty** > Adapted level of documentation; Training  
**Possible necessary sponsor presence during administration or in any upstream collection procedure** > justification
- Traceability**  
**If human origin cells/ tissues** > Bidirectional traceability system (anonymous coding); 30 years data keeping; Role and responsibilities of manufacturer, sponsor and investigator & location of traceability records to be documented
- Retention of samples**  
**Materials' scarcity** > Autologous ATMPs and certain allogeneic ATMPs: justified not to keep samples; Possible sampling strategy adaptation;  
**Short shelf-life** > Shorter retention period; Manufacturer to consider conditions for prolonging shelf-life;  
**Samples cannot be kept** > Retained label Photographs or copies

### Protection of CT subjects

**Uncertainties, novelty...**  
**Informed consent:** CT participant information on all risks, e.g., treatment failure, irreversible ATIMP nature...

### Safety reporting

**ATMPs characteristics > safety concerns** > Adapted reporting forms & data capture systems; List of safety issues; Sponsor to provide information/ training to investigator for adverse events reporting; Foreseen long-term follow-up to include reporting of adverse events

## CONCLUSION

Very useful ATMPs specific guidelines for clinical trials covering many different aspects and all currently identified challenges  
Necessary case by case evaluation of the various aspects of ATIMP's clinical trials mainly due to variability of starting materials and specific characteristics of each ATMP. Various levels of justification and documentation to be provided for clinical trials authorization  
→ Particularly relevant to engage in a pre-CT application meeting with regulatory agencies, such as the French National Agency (ANSM) as it is proposed in France



**III**

**Market Access/  
Hospital Exemption**

## The Marketing Authorisation of Advanced Therapy Medicinal Products in the European Union

**A. MAHALATCHIMY, L.-S. GILBERT, A. DELAGE, O. NÈGRE**, The Marketing Authorisation of Advanced Therapy Medicinal Products in the European Union, International Society for Cell & Gene Therapy 2023 Paris Annual Meeting, Paris, France, 31 May- 3 June 3 2023 (POSTER available at <https://shs.hal.science/halshs-04290539v1>);

Abstract published in Cytotherapy Volume 25, Issue 6, Supplement, May 2023, Pages S160–S161. [https://doi.org/10.1016/S1465-3249\(23\)00433-4](https://doi.org/10.1016/S1465-3249(23)00433-4)

### Abstract

Advanced Therapy Medicinal Products (ATMPs) is a European classification of medicinal products based on genes, cells and tissues specifically regulated in the European Union (EU) from the entry into force of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on ATMPs. Any company wishing to market ATMPs within the EU must hold a Marketing Authorisation (MA) issued by the European Commission under the “centralised procedure”, after a single application to the European Medicines Agency (EMA) and its scientific assessment by the Committee for Advanced Therapies. The purpose of the MA is to ensure high quality, safety and efficacy for ATMPs, with a positive risk-benefit balance, to be commercialised. The MA is valid in the EU Member States, Iceland, Norway and Liechtenstein for a five-years period. From the adoption of the EU regulation, 24 ATMPs have been granted a marketing authorisation in the EU and the European Commission decision is pending for another one. There has been a clear increase in approvals from 2018, and most approved ATMPs are gene therapy medicinal products. Almost half of them benefited from expediting pathways or regulatory support schemes for (innovative) medicines to be commercialised in the EU. Nevertheless, MA has been withdrawn or not renewed for 7 of them. This poster will present the European regulatory requirements and pathways for ATMPs to obtain marketing authorisation, and discuss the challenges of their commercialisation.

# The marketing authorisation of Advanced Therapy Medicinal Products under the regulation of the European Union

Aurélie Mahalatchimy<sup>1</sup>, Luc-Sylvain Gilbert<sup>2</sup>, Auxane Delage<sup>3</sup>, Olivier Nègre<sup>4</sup>

<sup>1</sup>EuroGCT Deputy coordinator and WP4 leader, Permanent Researcher in law at the French National Centre for Scientific Research (CNRS, CR), Law Faculty, UMR 7338 International, Comparative and European laws (DICE), CNRS, Aix Marseille Univ, Toulon Univ, Aix-en-Provence, France; <sup>2</sup>EuroGCT Information Officer on ELSI, Research Engineer and PhD student in law, Law Faculty, UMR 7338 DICE CERIC, CNRS, Aix Marseille Univ, Toulon Univ, Aix-en-Provence, France; <sup>3</sup>EuroGCT Information Officer on Ethical, legal & societal issues (ELSI), Research Engineer and PhD student in law, Law Faculty, UMR 7338 DICE CERIC, CNRS, Aix Marseille Univ, Toulon Univ, Aix-en-Provence, France; <sup>4</sup>Biotherapy Partners Paris, France EuroGCT Member of the General Committee, Management Group Deputy Coordinator, WP4 Co-Leader, Board Member of the French Society of Cell and Gene Therapy (SFCGT), Chief Scientific Officer at Synti Immune, Expert in Cell and Gene Therapy.

**Acknowledgments:** This work has been supported by the European Union's Horizon 2020 research and innovation programme (GA No 665241) and by ANR-funded I-Biolex project (ANR-20-CE26-0007-01).

## BACKGROUND & AIM

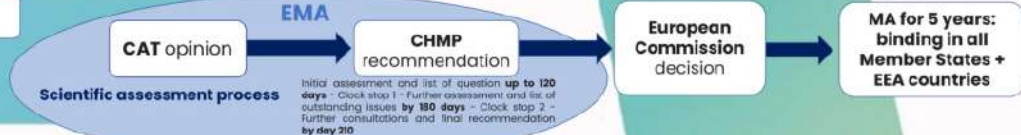
Advanced Therapy Medicinal Products (ATMPs) is a European classification of medicinal products based on genes, cells and tissues specifically regulated in the European Union (EU) from the entry into force of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on ATMPs.

Any company wishing to market ATMPs within the EU must hold a Marketing Authorisation (MA) issued by the European Commission under the "centralised procedure" (CP), after a single application to the European Medicines Agency (EMA) and its scientific assessment involving notably the Committee for Advanced Therapies (CAT). The purpose of the MA is to ensure high quality, safety and efficacy for ATMPs, with a positive risk-benefit balance, to be commercialised.

The CP is the standard procedure to allow MA holders to market ATMPs throughout the EU. The MA shall be refused, suspended or withdrawn if the quality and the safety of the ATMPs is insufficient and if the risk-benefit balance is not favourable. Moreover, expediting MA pathways and regulatory tools have been developed to provide more flexibility and accelerate ATMPs access to the market while other pathways exist for patients to access ATMPs without MA. The latter are alternative to standard CP and possible under strict conditions only.

## STANDARD MA

Expensive and time-consuming process which can delay patients' access to ATMPs although provides a wider market access



CHMP: Committee for Medicinal Products for Human Use, EEA: European Economic Area

## PROCEDURES AND PROGRAMMES FOR EARLIER ACCESS

### EXPEDITING MARKETING AUTHORISATION PATHWAYS

	Accelerated Assessment (AA)	Conditional MA	MA under Exceptional Circumstances
Basis	Article 14(9) Reg 726/2004	Article 14a Reg 726/2004	Article 14(b) Reg 726/2004
What	Assessment time for MA ≤ 150 days	Less complete data	Inability to provide comprehensive safety & efficacy data for objective & verifiable reasons
Why		Early access	
How	Major interest for public health (unmet medical needs) Standard MA criteria	Seriously debilitating or life-threatening diseases, emergency situations, orphan drugs, unmet medical needs Standard MA criteria	Rare condition or collection of full information or data is not possible in the state of scientific knowledge or unethical
Who	MA Applicant to European Medicines Agency		
When	Before submission of MA BUT to be discussed earlier via PRIME	Before submission of MA BUT to be discussed earlier via scientific advice / protocol assistance	

### SPECIFIC REGULATORY SCHEMES

	PRIME	ATMP PILOT for academic & non-profit organisations
What	An enhanced interaction & early dialogue to optimise development plans & speed-up evaluation of promising medicines	Enhanced regulatory support for up to five selected ATMPs to optimise their development
Why	To support medicine development	To support translation of basic research into medicine
Criteria	Unmet/high medical need	
How	Fostering early dialogue to improve clinical trials designs	Guiding through the regulatory process
Who	Potential candidate for AA to dedicated person at EMA	Academic/Non-profit ATMP developers to national competent authority or EMA
When	Use of existing routes of approval, especially AA Clinical stages of development (or earlier for academics and SMEs)	Possible to use existing support scheme (e.g., PRIME) Early stages of development (from best practice principles for manufacturing to planning clinical developments)

SME: Small and Medium Enterprises, PRIME: Priority medicines

## OTHER PATHWAYS FOR PATIENTS' ACCESS TO ATMPs

	Compassionate use: Groups of patients	Compassionate use: Named-patients basis	ATMP Hospital Exemption
Basis	Article 83 of Regulation 726/2004	Article 51 of Directive 2001/83/EC	Article 28.2 of Regulation 1394/2007
What	Under strict condition for seriously ill groups of patients (life-threatening, long-lasting or seriously debilitating illnesses), Undergoing clinical trials or MAA process	For a bona fide unsolicited order, with specifications of an authorised healthcare professional, & for use by an individual patient	ATMP prepared on a non-routine basis, specific quality standards, & used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, to comply with an individual medical prescription
Why	To facilitate & improve access to compassionate use programmes	To fulfil special needs of patients, including without ongoing clinical trials	To enable patients to receive ATMPs under controlled conditions
How	EMA/CHMP recommendations & national rules	National rules	National rules but traceability & pharmacovigilance requirements and quality standards equivalent to ATMPs going through the MA pathway
Who	National competent authority to EMA & Applicant to National competent authority	Applicant to National competent authority	Applicant to National competent authority

## The 25 authorised ATMPs in the EU

Name	Type	Domain	MA Year	MA Type	Current status
ChondroCelect	TEP	Orthopaedic	2009	Standard	Withdrawn, 29-07-2018
Glybera	GTMP	Gastrology	2012	Exceptional	Withdrawn, 28-10-2017
MACI	Comb. TEP	Orthopaedic	2013	Standard	Withdrawn, 1-7-2018
Provenge	CTMP	Oncology	2013	Standard	Withdrawn, 6-5-2015
Holoclar	TEP	Ophthalmology	2015	Conditional	Positive
Imyigic	GTMP	Oncology	2015	Standard	Positive
Strimvelis	GTMP	Immunology	2016	Standard	Positive
Zalmaxis	CTMP	Graft vs. host	2016	Conditional	Withdrawn, 9-10-2019
Sphearos	TEP	Orthopaedic	2017	Standard	Positive
Aloflisel	TEP	Gastrology	2018	Standard	Positive
Yescarta	GTMP	Immunocellular cancer	2018	Standard (PRIME)	Positive
Kymriah	GTMP	Immunocellular cancer	2018	Standard (PRIME)	Positive
Luxturna	GTMP	Ophthalmology	2018	Standard	Positive
Zynegis	GTMP	Beta-Thalassaemia	2019	Conditional/Accelerated (PRIME)	Withdrawn, 24-3-2022
Zalgensma	GTMP	Muscular Atrophy	2020	Conditional/Accelerated (PRIME)	Positive
Libmeldy	GTMP	Leukodystrophy, Metachromatic	2020	Accelerated	Positive
Tecartus	GTMP	Lymphoma, Mantle-Cell	2020	Conditional/Accelerated (PRIME)	Positive
Skyssona	GTMP	Cerebral adreno leuko-dystrophy	2021	Accelerated (PRIME), reverted to Standard	Withdrawn, 16-11-2021
Abecma	GTMP	Cancer of plasma cells	2021	Conditional/Accelerated (PRIME)	Positive
Ilirysart	GTMP	Blood cancer	2022	Accelerated (PRIME)	Positive
Upstaza	GTMP	Amino Acid Metabolism, Inborn errors	2022	Exceptional	Positive
Carvykti	GTMP	Multiple Myeloma cancer of the bone marrow	2022	Conditional (PRIME)	Positive
Rocovian	GTMP	Haemophilia A	2022	Conditional	Positive
Elvalfolo	CTMP	Lymphoproliferative Disorders	2022	Exceptional (PRIME)	Positive
Hemigenix	GTMP	Haemophilia B	2023	Conditional (PRIME)	Positive

Latest update - March 2023, TEP: Tissue Engineered Product, GTMP: Gene Therapy Medicinal Product, CTMP: Cell Therapy Medicinal Product, MA: Marketing Authorisation

## RESULTS

- Clear increase in approvals from 2018
- Most approved ATMPs are gene therapy medicinal products
- Half of authorised ATMPs benefited from expediting pathways or regulatory support schemes for innovative medicines

## CONCLUSION

Even if the EU supports and fosters ATMPs' research, development, and access to market with regulatory tools, patients access to effective and affordable ATMP is limited by the high average cost per patient, the withdrawal of authorised ATMPs from MA holder mostly for commercial reasons, and the differences between healthcare systems and reimbursement strategies of the different Member States.

Although the standard procedure and the expediting MA pathways provide the widest commercialisation of ATMPs in Europe, patients' access to ATMPs is dependent on MA granting and on the MA holder strategy to make the product available in Europe. The latter is linked to the agreement(s) on pricing and reimbursement to provide affordable ATMPs as well as an acceptable financial benefit, including return on investment, for the MA holder.

Patients can also access ATMPs, thanks to other pathways, alternative to MA and possible under strict conditions only. However, depending on how these other pathways can be used according to the applicable national heterogeneous rules (e.g. hospital exemption), they could also lead to unfair competition regarding the high requirements for MA

## Expediting marketing authorization pathways for patients' access to advanced therapies

V. ROBY, L-S. GILBERT, V. BRUNEL, A. DELAGE, A. MAHALATCHIMY, Expediting marketing authorization pathways for patients' access to advanced therapies, EAHL 2024, 18-20 September 2024, Warsaw, Poland (POSTER available at <https://shs.hal.science/halshs-04842656v1>)

### Abstract

Medicinal products based on genes, cells and tissues of human or animal origin are being developed to treat severe diseases that conventional treatments have failed to treat or that have no available and satisfactory treatments, such as rare, genetic, or neurodegenerative diseases.

The risks they raise as innovative and complex medicines but also the therapeutic promises they offer have led to their specific regulation as Advanced Therapy Medicinal Products (ATMPs) in the European Union (EU). Indeed, they are especially submitted to the centralised procedure of Marketing Authorisation (MA) issued by the European Commission. This procedure aims not only to ensure high quality, safety and efficacy for ATMPs with a positive risk-benefit balance to be commercialised, but also a wide access to these medicines for EU patients. Nevertheless, this procedure alone is not always sufficient to allow the commercialisation of ATMPs, and many of them require expediting pathways or regulatory support schemes for innovative medicines to be commercialised. From the adoption of the EU regulation, 25 ATMPs have been granted a MA in the EU. Although there has been a clear increase in approvals from 2018, MA has been withdrawn or not renewed for 7 of them.

Starting from the centralised procedure as the strongest and first legal procedure for the widest and safest patients access to these innovative medicines, this poster will provide an overview of the European MA expediting pathways and of their use, for ATMPs to be accessible, and discuss the challenges of their quick but safe commercialisation.

# The expediting marketing authorisation pathways for patients' access to advanced therapies

Valentin Roby<sup>1</sup>, Luc-Sylvain Gilbert<sup>2</sup>, Valentin Brunel<sup>3</sup>, Auxane Delage<sup>4</sup>, Aurélie Mahalatchimy<sup>5</sup>

<sup>1</sup> Research Engineer in law, EuroGCT and I-Biolex research projects, Law Faculty, Aix Marseille Univ, CNRS, DICE, CERIC, Aix-en-Provence, France; <sup>2</sup> Study Engineer at the French National Centre for Scientific Research (CNRS), Law Faculty, Aix Marseille Univ, CNRS, DICE, CERIC, Aix-en-Provence, France; <sup>3</sup> EuroGCT Information Officer on Ethical, Legal & Societal Issues (ELSI), Research Engineer and PhD student in law, Law Faculty, Aix Marseille Univ, CNRS, DICE, CERIC, Aix-en-Provence, France; <sup>4</sup> Research Engineer and PhD student in law, EuroGCT Information Officer on Ethical, Legal & Societal Issues (ELSI), Research Engineer and PhD student in law, Law Faculty, Aix Marseille Univ, CNRS, DICE, CERIC, Aix-en-Provence, France; <sup>5</sup> CNRS Permanent Researcher in law (CR), EuroGCT Deputy coordinator and WP4 leader, I-Biolex PI Law Faculty, Aix Marseille Univ, CNRS, DICE, CERIC, Aix-en-Provence, France.

**Acknowledgments:** This work has been supported by the European Union's Horizon 2020 EuroGCT project (GA No 965241) and by ANR-funded I-Biolex project (ANR-20-CE26-0007-01).

## BACKGROUND & AIM

Medicinal products based on genes, cells and tissues of human or animal origin are being developed to treat severe diseases that conventional treatments have failed to treat or that have no available and satisfactory treatments, such as rare, genetic, or neurodegenerative diseases.

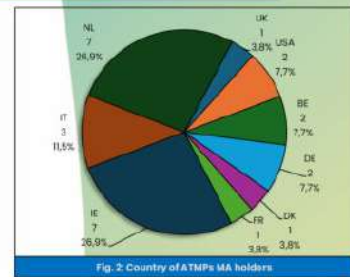
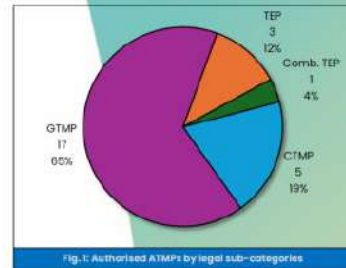
The risks they raise as innovative and complex medicines but also the therapeutic promises they offer have led to their specific regulation as Advanced Therapy Medicinal Products (ATMPs) in the European Union (EU). ATMPs include 4 legal sub-categories : Cell-therapy medicinal products (CTMP), Gene therapy medicinal products (GTMP), Tissue engineered products (TEP) and Combined (Comb.) ATMPs. They are especially submitted to the centralised procedure of Marketing Authorisation (MA) issued by the European Commission. This procedure aims not only to ensure high quality, safety and efficacy for ATMPs with a positive risk-benefit balance to be commercialised, but also a wide access to these medicines for EU patients. To date, 26 ATMPs have been granted a MA in the EU. Nevertheless, this procedure alone is not always sufficient to allow the commercialisation of ATMPs and many of them require expediting pathways or regulatory support schemes for innovative medicines to be commercialised.

What are these expediting pathways and how much have they been used for ATMPs ?

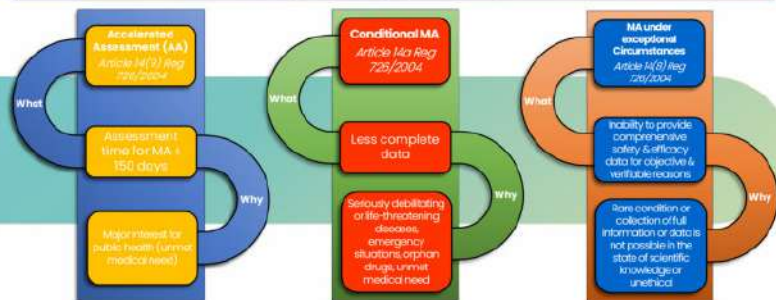
## Overview of the 26 authorised ATMPs in the EU

List of ATMPs

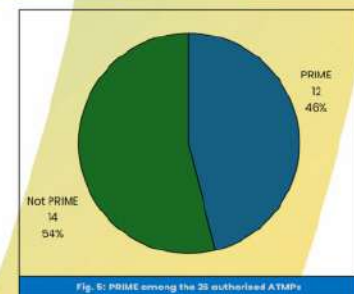
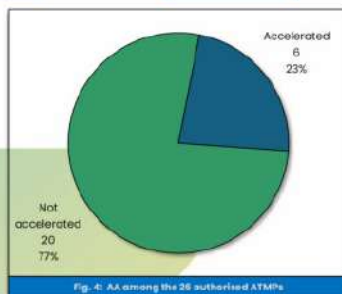
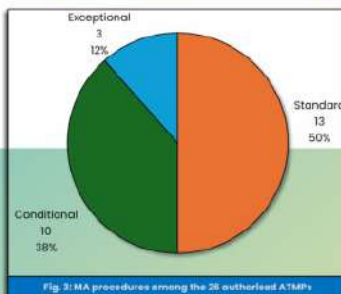
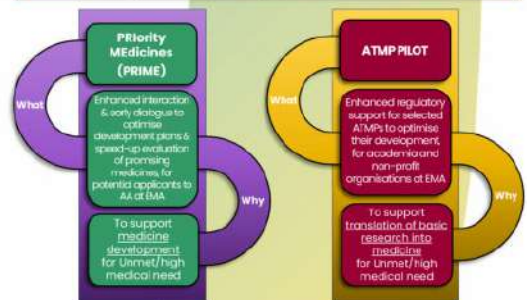
Name	Type	Domain	MA Year	Current status
ChondroCelect	TEP	Orthopaedic	2009	Withdrawn, 29/07/2016
Glybera	GTMP	Gastrology	2012	Withdrawn, 28/10/2017
MACI	Comb. TEP	Orthopaedic	2013	Withdrawn, 01/07/2018
Provenge	CTMP	Oncology	2013	Withdrawn, 06/05/2015
Holoclar	TEP	Ophthalmology	2015	Positive
Imlygic	GTMP	Oncology	2015	Positive
Strimvelis	GTMP	Immunology	2016	Positive
Zalmoxis	CTMP	Graft vs host	2016	Withdrawn, 09/10/2019
Spherox	TEP	Orthopaedic	2017	Positive
Alofisel	CTMP	Gastrology	2018	Positive
Yescarta	GTMP	Immunocellular cancer	2018	Positive
Kymriah	GTMP	Immunocellular cancer	2018	Positive
Luxturna	GTMP	Ophthalmology	2018	Positive
Zynteglo	GTMP	Beta-Thalassemia	2018	Withdrawn, 24/03/2022
Zalgensma	GTMP	Muscular Atrophy	2020	Positive
Urbemedy	GTMP	Metachromatic Leukodystrophy	2020	Positive
Tecartus	GTMP	Lymphoma, Mantle-Cell	2020	Positive
Skysena	GTMP	Cerebral adreno leuko- dystrophy	2021	Withdrawn, 18/11/2021
Abeema	GTMP	Multiple Myeloma cancer of the bone marrow	2021	Positive
Breyanzi	GTMP	Blood cancer	2022	Positive
Carvykti	GTMP	Multiple Myeloma cancer of the bone marrow	2022	Positive
Upstaza	GTMP	Amino Acid Metabolism, Inborn Errors	2022	Positive
Roctavian	GTMP	Haemophilia A	2022	Positive
Ebvallo	CTMP	Lymphoproliferative Disorders	2022	Positive
Hemgenix	GTMP	Haemophilia B	2023	Positive
Casgevy	GTMP	Beta-Thalassemia and sickle cell disease	2024	Positive



## Expediting pathways



## Regulatory Support schemes



## RESULTS

- Clear increase in approvals from 2018 in various medical domains
- Most approved ATMPs are gene therapy medicinal products
- NL, where is established the European Medicines Agency from Brexit, and IE are the countries of most of MA holders among the authorised ATMPs
- Half of authorised ATMPs benefited from expediting pathways or regulatory support schemes for innovative medicines
- BUT MA withdrawn or not renewed for 7 ATMPs out of 26 authorized ATMPs

## DISCUSSION/CONCLUSION

Even if the EU supports and fosters ATMPs' research, development, and access to market with regulatory tools, patients access to effective and affordable ATMP is limited by the high average cost per patient, the withdrawal of authorised ATMPs from MA holder mostly for commercial reasons, and the differences between healthcare systems and reimbursement strategies of the different Member States. Although the standard procedure and the expediting MA pathways provide the widest commercialisation of ATMPs in Europe, patients' access to ATMPs is dependent on MA granting and on the MA holder strategy to make the product available in Europe. The latter is linked to the agreement(s) on pricing and reimbursement to provide affordable ATMPs as well as an acceptable financial benefit, including return on investment, for the MA holder. Patients can also access ATMPs, thanks to other pathways, alternative to MA and possible under strict conditions only. However, depending on how these other pathways can be used according to the applicable national heterogeneous rules (e.g., hospital exemption), they could also lead to unfair competition regarding the high requirements for MA granting.

## What regulatory pathways for health technologies using both medical devices and T&C in the European Union?

V. ROBY, A. DELAGE, L.-S. GILBERT, A. BOTTACCI, A. MAHALATCHIMY, What regulatory pathways for health technologies using both medical devices and T&C in the European Union?, ESGCT 2025, 7-10 October 2025, Seville, Spain (POSTER available at <https://shs.hal.science/halshs-05314492v1>)

### Abstract

Medical applications of tissues and cells (T&C), whether from human or animal origin, can be various. While the legal distinction between transplants and Advanced Therapy Medicinal Products (ATMPs) has been widely commented, the legal classification of health technologies based on the association between medical devices (MD) and T&C is poorly explored and known. Yet, from their collection to the patient's administration, they have to follow the appropriate regulatory pathways in accordance with their legal classification. First, the MD and the T&C have to comply with the respectively applicable European legislations: the regulations on MD and on substances of human origin for T&C of human origin. Second, when T&C are substantially manufactured into medicinal products, they would be categorised as biological medicinal products, most of the time as ATMPs. The association between T&C and MD may be external, and MD can be companion diagnostics to a transplant or an ATMP. Parallel regulatory pathways have to be followed by each product. But the association between T&C and medical devices may also be integrative. Depending on what is regulatorily considered as the dominant part in the overall product, the latter can be either a medicine or a MD. On the one hand, if the T&C are the dominant part, the overall product should be a combined ATMP. This is a hybrid sub-category of ATMP that should encompass certain organoids. On the other hand, if the action of the T&C is only ancillary to that of the device, the overall product should be a MD. This latter type of products is not only defined in contrast to medicinal products, they are also following a completely different regulatory pathway to reach the market. While any ATMPs' developer has to go through the centralised procedure to obtain a marketing authorisation (granted by the European Commission after evaluation by the European Medicines Agency), MDs' manufacturers, on the other hand, have to "certify" their products. This requires the involvement of a Notified body – a non-state entity designated by a member state for the assessment of certain MDs – before commercialising MDs based on T&C. And while the European legislation distinguishes between gene therapy, cell therapy, tissue engineering, and combined ATMPs among ATMPs, it divides MDs into classes, depending on their purpose and their risk. Thus, their two distinct regulatory pathways are worst to be known, as each one has its own specific requirements. The distinction criteria between MDs and ATMPs are based on the viability of the tissues or cells, and primary or ancillary action of each part of the overall product. Yet, navigating through the various legal texts regarding definitions and scopes to identify the legal classification and applicable regulatory pathway(s) of health technologies may be challenging, especially as the association between MD and T&C adds another layer of complexity. This poster will clarify and discuss the regulatory pathways applicable to health technologies using T&C of human or animal origin, from the collection of the biological starting materials to the commercialisation of the final health technologies.



# WHAT REGULATORY PATHWAYS FOR HEALTH TECHNOLOGIES USING BOTH MEDICAL DEVICES AND TISSUES AND CELLS IN THE EUROPEAN UNION?

Valentin Roby<sup>1</sup>, Auxane Delage<sup>2</sup>, Luc-Sylvain Gilbert<sup>3</sup>, Adrien Bottacci<sup>4</sup>, Aurélie Mahalatchimy<sup>5</sup>

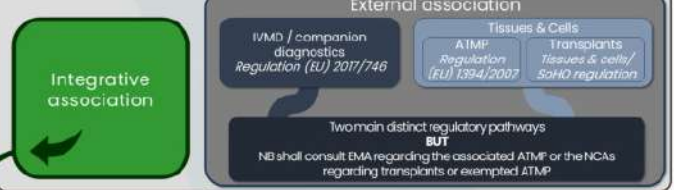
<sup>1</sup> Research Engineer in law, EuroGCT and i-BioLex research projects, Law Faculty, Aix Marseille Univ, CNRS, DICE, CERIC, Aix-en-Provence, France; <sup>2</sup> EuroGCT Information Officer on Ethical, Legal & Societal Issues, Research Engineer and PhD student in law, Law Faculty, Aix Marseille Univ, CNRS, DICE, CERIC, Aix-en-Provence, France; <sup>3</sup> EuroGCT Information Officer on Ethical, Legal & Societal Issues, Research Engineer in law, Law Faculty, Aix Marseille Univ, CNRS, DICE, CERIC, Aix-en-Provence, France; <sup>4</sup> PhD student in law, CNRS DICE, ADES CERIC, Aix-en-Provence, France; <sup>5</sup> Permanent Researcher in law at the French National Centre for Scientific Research (CNRS, chargé de recherche), Law Faculty, Aix Marseille Univ, CNRS, DICE, CERIC, Aix-en-Provence, France; EuroGCT Deputy coordinator and WPA leader.

**Acknowledgments:** This work has been supported by the European Union's Horizon 2020 research and innovation programme EuroGCT (GA: 985241) and by ANR-funded i-BioLex project (ANR-20-CE26-0007-01).

## Introduction

Medical applications of tissues & cells, whether from human or animal origin, can be various. The legal classification of health technologies based on the association between Medical Devices (MD) or In Vitro Medical Devices (IVMD) and tissues & cells is poorly explored and known. Yet from their collection to the patient administration, they must go through the appropriate regulatory pathways according to their legal classification. Knowing the applicable regulatory pathways is crucial for complying with legal and regulatory requirements and adapting development strategies. This poster clarifies and discusses the regulatory pathways applicable to the associations between MD and tissues & cells, be they of human or animal origin, from the collection of the biological starting materials to the commercialisation of the final health technologies.

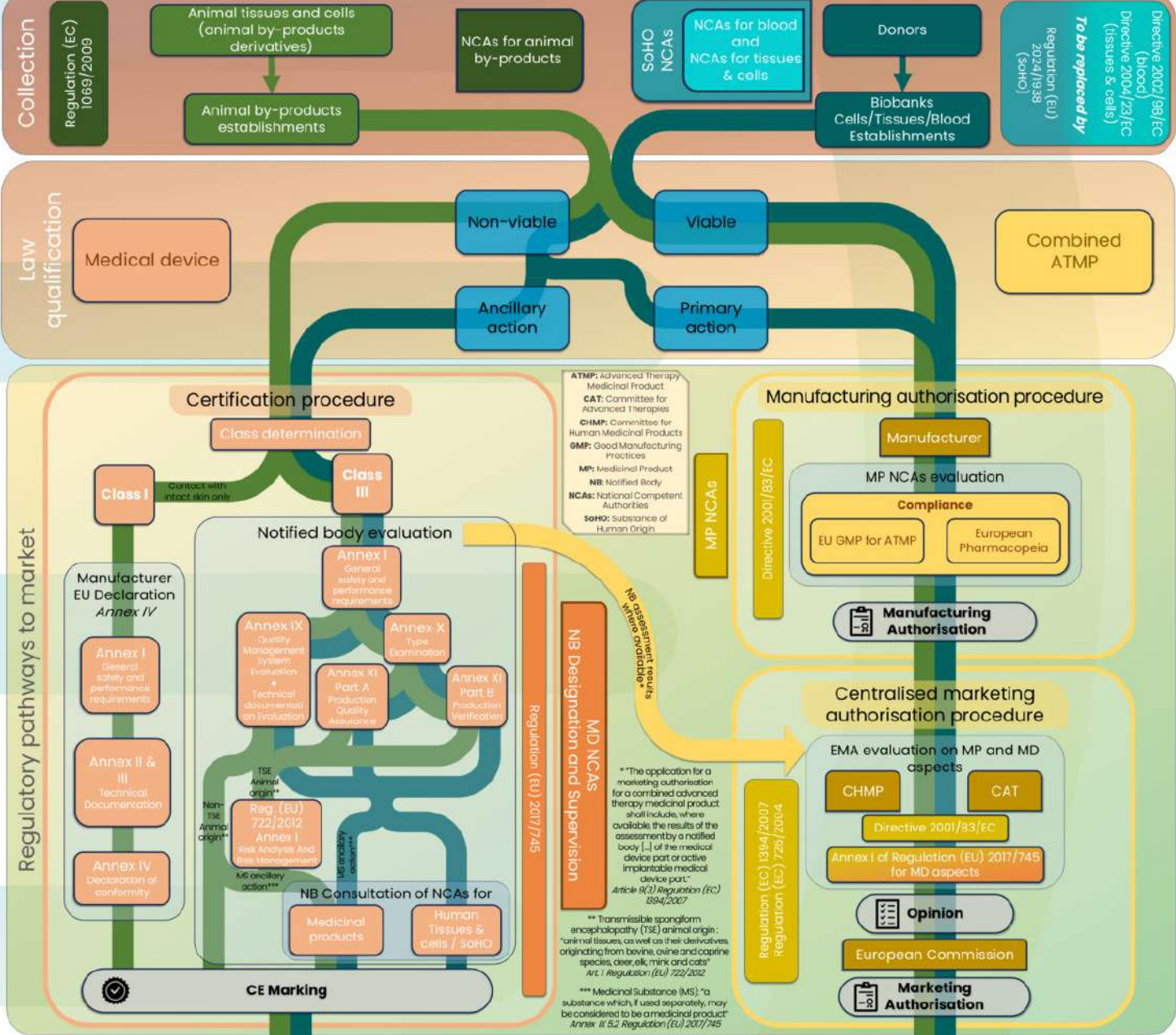
## Association of tissues & cells and medical devices



Tissues and cells of Animal origin

Combined Products

Tissues and cells of Human origin



ATMP: Advanced Therapy Medical Product  
 CAT: Committee for Advanced Therapies  
 CHMP: Committee for Human Medicinal Products  
 GMP: Good Manufacturing Practices  
 MP: Medicinal Product  
 NB: Notified Body  
 NCA's: National Competent Authorities  
 SoHO: Substance of Human Origin

MD NCA's  
 NB Designation and Supervision  
 Regulation (EU) 2017/745

\* 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 [...] of the medical device part or active implantable medical device part.  
 Article 9(3) Regulation (EC) 1394/2007

\*\* Transmissible spongiform encephalopathy (TSE) animal origin: "animal tissues, as well as their derivatives originating from bovine, ovine and caprine species, deer, elk, mink and coon".  
 Art 1 Regulation (EU) 722/2012

\*\*\* Medicinal Substance (MS): "a substance which, if used separately, may be considered to be a medicinal product"  
 Annex II.5.2 Regulation (EU) 2017/745

## Commercialisation and post-market surveillance & vigilance

## Conclusion

Significantly different from one another, the regulatory pathways to commercialisation of health products combining medical devices and tissues & cells also appear to be complex, involving several cross-references between distinct regulations and cross-linked interventions of their respective actors. If such complexity reflects the EU objective to guarantee health safety for patients to access (new) biomedical technologies, it is also challenging for appropriate regulatory compliance in their development. Nevertheless, three tools have been developed to address this challenge:

- **Dialog and support mechanisms** for developers to interact with regulators at each phase of product development: e.g. possibility to seek advice from NCA's, NB's and/or the EMA.
- **Strengthened Coordination** between Member States' and the European Commission: e.g. Medical Device Coordination Group, and SoHO Coordination Board.
- **Guidance documents** are regularly issued and updated on technical, scientific and regulatory aspects: e.g. EMA, Q&A for applicants; marketing authorisation holders of medicinal products and notified bodies with respect to the implementation of the Regulations on medical devices and in vitro diagnostic medical devices (Regulations (EU) 2017/745 and (EU) 2017/746), EMA, 3/19/2019 Rev. 5: 30 January 2025 and EMA, Guideline on quality documentation for medicinal products when used with a medical device, EMA/C/MP/CPWP/BWP/22895/2019, 22 July 2021.



## ATMPs: exceptional manufacturing returns to the patient's bedside

J. VÉLAN, J. MAGALON, C. DUMOULIN, S. RABARIMERIARIJAONA, L. AGNELLI, M. VELIER, F. SABATIER, A. MAHALATCHIMY, ATMPs: exceptional manufacturing returns to the patient's bedside, ESGCT 2025, 7-10 October 2025, Seville, Spain (POSTER available at <https://shs.hal.science/halshs-05314447v1>)

### Abstract

Since the publication of the European Regulation (No. 1394/2007) on Advanced Therapy Medicinal Products (ATMPs) in 2007, innovative therapies based on genes, cells, or tissues have reshaped the pharmaceutical landscape. While offering significant opportunities for economic and medical advances, their complex manufacturing raises specific issues on quality and regulatory issues. Detailed guidelines on Good Manufacturing Practices (GMP) specifically tailored to ATMPs have been adopted by the European Commission and have been enforceable since 2017. They address new technological developments, scientific advances, and more suitable production and distribution pathways. To date, 27 ATMPs have obtained a marketing authorization in Europe, but most are still at the clinical trial stage although they could provide very promising options for addressing unmet medical needs. Making ATMPs accessible to patients remains challenging due to factors such as high cost, the specialized nature of ATMPs manufacturing including stringent safety and efficacy. Moreover, current healthcare infrastructures often require substantial adaptations to accommodate the logistical demands of these treatments. The Hospital Exemption (HE) is a regulatory provision of the European Regulation, that allows the use of certain ATMPs without formal central marketing authorization provided specific criteria are met: a medical prescription for an individual patient, a use within the same Member State, in a hospital setting under the exclusive responsibility of a medical practitioner, a GMP compliant manufacturing. HE implementation and oversight are regulated at the national level by the competent authority of each EU Member State. It provides a practical solution for bypassing the lengthy centralized authorization and facilitating timely access to innovations stemming from academic research and hospital initiatives. In France, a significant regulatory evolution in the field of ATMPs has been recently introduced by the decree on February 16, 2022, pursuant to French Law No. 2021-1017. It establishes a sub-exemption mechanism within the broader HE framework, specifically designed to address the practical challenges of certain ATMPs derived from autologous cells or tissues and involving no substantial manipulation. It authorizes the preparation, distribution, and administration of ATMPs, within the same medical procedure as the procurement of autologous tissues or cells used in their composition, without requiring a specially authorized manufacturing establishment, providing prior validation by the French National Agency for Medicines Safety (ANSM). By formalizing a legal framework for decentralized, bedside production, the decree aligns regulation with the practical realities of personalized medicine, favors more agile healthcare organization and fasters patient access. We aim to present and discuss the first application of this innovative regulatory framework within the MICROPREP III clinical trial (EudraCT No 2023-507683-40). This trial is designed to evaluate in 180 patients the efficacy of intra-articular injections of autologous microfat, optionally combined with autologous platelet-rich plasma (PRP), as an adjunctive therapy for patients with Knee osteoarthritis. The application of the single-step autologous ATMPs exemption needed to implement new measures and agreements between clinicians and manufacturer to ensure compliance to GMP guidelines and ATMPs quality remaining under the responsibility of the authorized establishment despite delocalization.



I-BIOLEX



# ATMPs: exceptional manufacturing returns to the patient's bedside

J. Véran<sup>1</sup>, J. Magalon<sup>1</sup>, C. Dumoulin<sup>1</sup>, S. Rabarimeriarijaona<sup>1</sup>, L. Agnelli<sup>3</sup>, M. Velier<sup>1</sup>, F. Sabatier<sup>1</sup>, A. Mahalatchimy<sup>2</sup>

<sup>1</sup>Cell therapy/Advanced Therapy Medicinal Products' Unit, Center for Clinical Investigation in Biotherapy (INSERM CIC 1409), Marseille University Hospital (AP-HM), 13005 Marseille, France

<sup>2</sup>Law Faculty, Aix Marseille Univ, CNRS, DICE, CERIC, 13628 Aix-en-Provence, France

<sup>3</sup>Health Research Department, Marseille Public Hospital (AP-HM), 13005 Marseille, France

Acknowledgments. This work has been supported by the French National grant (Programme Hospitalier de Recherche Clinique 2020) and by ANR-funded I-Biotex project (ANR-20-CE26-0007-01).

## Introduction

Since the European Regulation (No. 1394/2007) on **Advanced Therapy Medicinal Products (ATMPs)**, only 30 ATMPs have obtained a marketing authorization in the European Union as at 30 September 2025, but most are still at the clinical trial stage.

- The European **Hospital Exemption (HE)** allows the use of certain ATMPs at the **national level** without formal central marketing authorization provided specific criteria are met: a non-routine basis preparation, a **medical prescription for an individual patient**, a use within the same Member State, in a hospital setting under the exclusive responsibility of a medical practitioner, a GMP compliant manufacturing, and compliance with traceability and pharmacovigilance requirements. It provides a practical solution for facilitating timely access to innovations stemming from national academic research and hospital initiatives.
- In France, the decree of **February 16, 2022**, has established a **sub-exemption** within the framework of HE, specifically designed to address the practical challenges only for ATMPs derived from **autologous cells or tissues** and not involving **any substantial manipulation**. It authorizes the manufacturing, distribution, and administration of these ATMPs, as part of the same medical procedure as the procurement of the autologous tissues or cells used in their composition, without requiring the manufacturing process to take place in a specially approved manufacturing facility (GMP classroom production), subject to prior validation by the French National Agency for Medicines and Health Products Safety (ANSM). By formalizing a legal framework for a so-called **"decentralized bedside" production**, the decree aligns regulations with the practical realities of personalized medicine, promotes a more agile organization of healthcare, and accelerates access to these ATMPs for patients.
- Within this new context, this poster presents the first French implementation of this new decree through the MICROPREP III clinical trial.

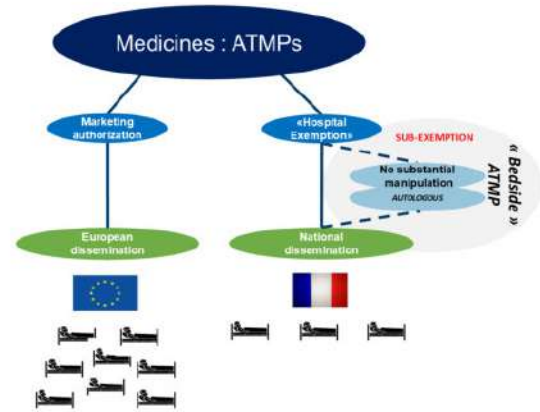


FIGURE 1 : Regulation frame for a national decentralized "bedside" sub-exemption ATMP manufacturing

## New measures for a "decentralized bedside autologous hospital exemption ATMP manufacturing"

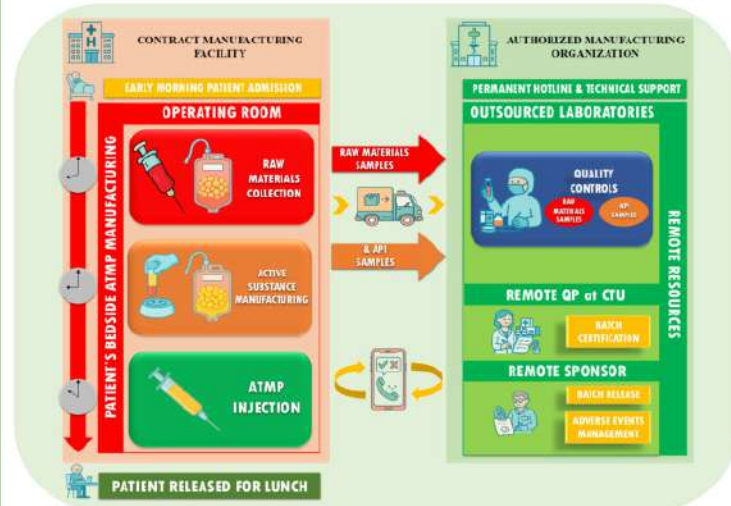


FIGURE 2 : MICROPREP III autologous "bedside" ATMP setup proposal

The First French therapeutic application of this innovative regulatory framework is addressed within the setup of **MICROPREP III clinical trial** (EudraCT No 2023-507683-40) authorized in May 2024.

- It is designed to evaluate in **180 patients** the efficacy of **intra-articular injections of autologous microfat**, optionally combined with **autologous platelet-rich plasma (PRP)**, as an **adjunctive therapy for patients with Knee osteoarthritis**.
- The application of the **single-step autologous ATMPs** exemption needed to implement new measures and agreements between clinicians and manufacturer to ensure compliance to GMP guidelines and ATMPs quality remaining under the responsibility of the authorized establishment despite delocalization (as mentioned in figure 2). The setup proposal by the national authorized manufacturing establishment consists in :
  - Using directly the operating room for the harvesting-manufacturing-administration of the "single step manufactured autologous ATMP"
  - Training and accrediting the medical staff
  - Centralizing quality controls
  - Centralizing the quality management at the authorized manufacturer level
  - Establishing fluid communication and traceability

## Expectations and Perspectives

- **Changes to ATMP's remote management rules**
  - Responsibilities between the manufacturer and the delegated staff
  - New relationship between the manufacturer and the physician
  - New measures in the quality management system
 ⇒ **Formal contract is a mandatory step**
- Challenges are expected regarding the standardization of protocols, requirement of trained personnel, reproducibility from site to site...
- Reduced ATMP's production time should increase patient treatment capacity (see figure 3), and is expected to be more suitable to supply & demand.
- More affordable expected cost to the healthcare system for a single batch of autologous ATMP
- ✓ How will the manufacturer and sponsor manage the risk management plan ?
- ✓ Will other EU countries apply new tools and rules to accelerate decentralized manufacturing at the patient's bedside under the hospital exemption for autologous ATMP, and how?

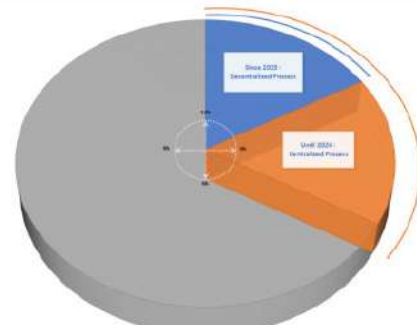


FIGURE 3 : Expected ATMP manufacturing time comparison from raw material collection to ATMP batch release between centralized process in GMP classroom (internal data extracted from GMP ATMP batches in Marseille Cell Therapy Unit) and decentralized process in the case of the "bedside" operating room production planned for MICROPREP III clinical trial.



**IV**

**Health Technology  
Assessment/  
Cost issues**

## The new European regulation on Health Technology Assessment: what changes for Advanced Therapy Medicinal Products?

**B. BARTOS, J. JUËT, F. TABOULET, A. MAHALATCHIMY**, The new European regulation on Health Technology Assessment: what changes for Advanced Therapy Medicinal Products?, European Society for Gene & Cell Therapy Congress 2022, Edinburgh, the UK, 11-14 October 2022 (POSTER available at <https://shs.hal.science/halshs-03901269v1>); Abstract published in Human Gene Therapy, Volume: 33 Issue 23-24: December 14, 2022, A1-A212. <http://doi.org/10.1089/hum.2022.29225.abstracts>

### Abstract

The new European regulation (EU) 2021/2282 on Health Technology Assessment (HTA), “a multidisciplinary process that summarises information about the medical, patient and social aspects and the economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased and robust manner”, has been adopted on 15 December 2021. It ensures an efficient use of resources and strengthens the quality of common HTA across the European Union, because until now, the assessment has been realized independently by each Member State. It will thus contribute to the improvement of the availability of health innovative technologies for EU patients that has been widely highlighted by the Council of the European Union and the European Parliament. It mainly establishes a Member State Coordination Group on HTA, a stakeholder network, whom the joint works and exchanges will be facilitated thanks to an IT platform. It also provides rules for joint clinical assessments, joint scientific consultations, horizon scanning for emerging technologies, further voluntary cooperation notably on non-clinical assessments on health technologies, i.e. “a medicinal product, a medical device, or medical and surgical procedures as well as measures for disease prevention, diagnosis or treatment used in healthcare”. The regulation shall apply progressively from 2025 to different types of health technologies, Advanced Therapy Medicinal Products (ATMPs) being the first targeted with cancer medicines. This poster will discuss the expected improvements for patients’ access to ATMPs regarding the forthcoming implementation of this new regulation.

# The new European regulation on Health Technology Assessment: what changes for Advanced Therapy Medicinal Products?

Blanka Bartos<sup>1</sup>, Joséphine Juët<sup>2</sup>, Florence Taboulet<sup>3</sup>, Aurélie Mahalatchimy<sup>4</sup>

<sup>1</sup> PhD Student in law, CREDIMI, Univ. of Burgundy, Dijon, 21077, France, <sup>2</sup> Student in Pharmaceutical Sciences, Univ. of Paul Sabatier- Toulouse 3, Toulouse, 31062, France., <sup>3</sup> Professor in Pharmaceutical Law and Health Economics, CERPOP (Center for Epidemiology and Research in POPulation health), UMR 1295 Inserm, Univ. of Paul Sabatier- Toulouse 3, Toulouse, 31062, France., <sup>4</sup> Permanent Researcher in law at the French National Centre for Scientific Research (CNRS), Faculty of Law, UMR 7318 International, Comparative and European law (DICE) CERIC, CNRS, Aix Marseille Univ., Toulon Univ. Pau & Pays de l'Adour Univ., Aix-en-Provence, 13628, France

Acknowledgement: This work has been supported by ANR-funded I-BioLex project (ANR-20-CE26-0007-01, coord. A. Mahalatchimy).

## Health Technology Assessment (HTA)

"A multidisciplinary process that summarises information about the medical, patient and social aspects and the economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased and robust manner."

Article 2.5) EU Regulation 2021/2282

➔ Evidence-based process enabling relative effectiveness assessment of new/ existing technologies

## Health technology?

"A medicinal product, a medical device or medical and surgical procedures as well as measures for disease prevention, diagnosis or treatment used in healthcare."

Article 3.I) Directive 2011/24/EU

➔ ATMPs are included

## PAST

- Independent assessments from national HTA bodies
- EUnetHTA (2006-2021): joint action, voluntary cooperation

BUT

- Redundancy of the evaluation process in the EU
- Misallocation of resources
- Inequitable access to new technologies

## PRESENT (2022)

Rolling implementation plan: preparatory phase

- Setting up the Coordination Group and the Stakeholder Network
- Drafting implementing & delegated acts, and guidance documents

- 2021-23: New EUnetHTA (2021)
- 2023-25: Member States remain responsible for drawing conclusions on added value for their health system and taking decisions on pricing & reimbursement. They can give additional multinational or simultaneous national scientific advice on a voluntary basis.

## FUTURE (from 2025)

Application of Joint Clinical Assessments:

- 2025: ATMPs, cancer drugs
- 2028: orphan drugs
- 2030: all medicines covered by Regulation scope

New HTA process:

- New **Coordination Group** managing HTA process
- **Secretariat** provided by the European Commission
- **National bodies** providing expert views on HTA
- Exchange of information with **stakeholder network**

- Increased quality of joint work
- Better allocation of resources: reduced expenses for national bodies and the EU
- Improved accessibility to ATMPs in the EU

## Clinical and non-clinical assessments

### Joint Clinical Assessments

➔ To be considered for any HTA at Member States level

**Description**  
Collection and analysis of clinical evidence about a health technology to determine its therapeutic value compared to other technologies already available or not.

**Goal**  
Quality, common source for States to determine pricing and reimbursement of health technology: **ATMPs<sup>+++</sup>**

### Voluntary Cooperation to exchange information, e.g., on non-clinical assessments

**Description**  
Allowing States to exchange information on non-clinical areas, for examples on organizational, ethical, legal, and economic matters, or on health technologies other than medicines and medical devices

**Goal**  
Going beyond the clinical scope: **ATMPs<sup>+++</sup>**

### Joint Scientific Consultations

➔ No legal effects on Member States

**Description**  
Early exchanges between industry and the Coordination Group.

**Goal**  
Advising on clinical studies designs to generate appropriate evidence: **ATMPs<sup>+++</sup>**

### Identification of Emerging Technologies (ATMPs)

➔ Coordination Group's Initiative

**Description**  
Reports on new technologies with potentially significant impact on patients, public health and healthcare systems.

**Goal**  
Anticipating issues to improve patient access: **ATMPs<sup>+++</sup>**

## Complementary tools

Support to industry

Support to national governments

## Remaining challenges:

- Building EU processes from national HTA experiences and feedback from experts
- Training more external expert / organisations on HTA in general, and on EU procedure(s)
- Organising HTA registries, raising awareness, collecting experiences
- Identifying / involving clinicians or patients (organisations' membership list, social networks, European Reference Networks, clinics in Pubmed...)

## The European regulation on Health Technology Assessment: balancing European and national levels

**A. MAHALATCHIMY, J. JUËT, B. BARTOS, F. TABOULET**, The European regulation on Health Technology Assessment: balancing European and national levels, International Society for Cell & Gene Therapy 2023 Paris Annual Meeting, Paris, France, 31 May- 3 June 3 2023 (POSTER available at <https://shs.hal.science/halshs-04290552v1>);

Abstract published in Cytotherapy Volume 25, Issue 6, Supplement, May 2023, Page S161. [https://doi.org/10.1016/S1465-3249\(23\)00434-6](https://doi.org/10.1016/S1465-3249(23)00434-6)

### Abstract

The European Health Technology Assessment (HTA) regulation was adopted at the end of 2021. HTA is “a multidisciplinary process that summarizes information about the medical, patient and social aspects and the economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased and robust manner”. While HTA has been conducted at national level, the regulation is provided for the harmonization of procedures to avoid redundancy of evaluation processes, misallocation of resources, and inequitable access to new technologies within the European Union (EU). The regulation will be implemented step by step, starting with Advanced Therapy Medicinal Products (medicines based on genes, cells, and tissues) and cancer drugs by 2025. Then it will be implemented for orphan drugs by 2028, and finally, for all medicines by 2030. Although EU Member States remain responsible for drawing conclusions on added value of health technologies for their health system and taking decisions on their pricing & reimbursement, a new coordination group (HTACG) is established at the EU level. The latter will manage the entire HTA process, relying on a Secretariat provided by the European Commission, national bodies providing their expert views on HTA, and a stakeholder network supporting its work. More specifically, the HTACG will coordinate the joint clinical assessments of health technologies and ensure the identification of emerging technologies. It will also carry out joint scientific consultations and facilitate the voluntary cooperation regarding the exchange of scientific information among Member States in the field of HTA. Therefore, this poster will present and discuss the balance established by the new regulation, between European and national activities in the field of HTA, in accordance with the Treaty provisions on the sharing of competences between the European Union and the Member States.

# The European regulation on Health Technology Assessment Balancing European and National Levels

Aurélie Mahalatchimy,<sup>1</sup> Joséphine Juët,<sup>2</sup> Blanka Bartos,<sup>3</sup> Florence Taboulet<sup>4</sup>

<sup>1</sup> Permanent Researcher in law at the French National Centre for Scientific Research (CNRS), Faculty of Law, UMR 7318 International, Comparative and European law (DICE) CERIC, CNRS, Aix Marseille Univ., Toulon Univ. Pau & Pays de l'Adour Univ., Aix-en-Provence, 13628, France. <sup>2</sup> Student in Pharmaceutical Sciences Master 2 Ethic and Research, Univ. Paul Sabatier - Toulouse 3, Toulouse, 31062, France. <sup>3</sup> PhD Student in law, CREDIMI, Univ. of Bourgogne, Dijon, 21077, France. <sup>4</sup> Professor in Pharmaceutical Law and Health Economics, CERPOP (Center for Epidemiology and Research in POPulation health), UMR 1295 Inserm, Univ. of Paul Sabatier- Toulouse 3, Toulouse, 31062, France. Acknowledgement: This work has been supported by ANR-funded I-BioLex project (ANR-20-CE26-0007-01, coord. A. Mahalatchimy).

In order to harmonize and optimize access to health technologies\*, including gene and cell therapies, the European Union changed its legislation with the adoption of a new regulation on Health Technology Assessment (HTA) in December 2021.

\*medicinal products, medical device or medical and surgical procedures, and measures for disease prevention, diagnosis or treatment used in healthcare

## What is HTA? EU Regulation 2021/2282

"A multidisciplinary process that summarises information about the medical, patient and social aspects and the economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased and robust manner."

P  
A  
S  
T

### HTA conducted at national level

+ EU initiative → EUnetHTA (2006-2021): joint action, voluntary cooperation between 25 States

Consequences

- Redundancy of evaluation process
- Misallocation of resources
- Inequitable access to new technologies

P  
R  
E  
S  
E  
N  
T

### Harmonization of procedure

**Regulation:** Rolling implementation plan, preparatory phase

- Setting up the **HTA Coordination Group (HTACG)** and the **Stakeholder Network**
- Drafting implementing & delegated acts, and guidance documents

+ New **EUnetHTA 21**: 13 States work to support the continuation of the HTA process at a European level

F  
U  
T  
U  
R  
E

### Step-by-step implementation

**2025**

Advanced Therapy Medicinal Products, cancer drugs

**2028**

Orphan medicines

**2030**

All health technologies

### National level

- **National bodies** provide expert views on HTA
- **Member States** remain responsible for:
  - drawing conclusions on added value of health technologies for their health system
  - taking decisions on their pricing & reimbursement

### European level

- **HTACG** manages the HTA process:
  - Joint clinical assessment (JCA)
  - Identification of emerging technologies
  - Joint scientific consultations
  - Voluntary cooperation
- **Stakeholder network** also supports HTACG's work, through exchange of scientific information
- **European Commission** supports HTACG's work, as the secretariat

- Regulation increases quality of joint work, and joint work increases quality of assessment.
- Better allocation of resources: reduced expenses for national bodies and the EU
- Improved accessibility to all medicines in the EU at medium and long term
- Among all processes, only joint clinical assessment will have to be taken into consideration at the national level.

### Remaining challenges

- Building EU processes from national HTA experiences and feedback from experts
- Training more external experts / organisations on HTA in general, and on EU procedure(s)

## Contracts for better access to Advanced Therapy Medicinal Products

**B. BARTOS**, Contracts for better access to Advanced Therapy Medicinal Products, European Society for Gene & Cell Therapy Congress 2022, Edinburgh, the UK, 11-14 October 2022 (POSTER) Abstract published in Human Gene Therapy, Volume: 33 Issue 23-24: December 14, 2022, A1-A212. <http://doi.org/10.1089/hum.2022.29225.abstracts>

### Abstract

The greater part of ATMPs is manufactured in a customized way with high technicity to offer promising health benefits with mostly a one-shot treatment for incurable, often orphan diseases. The scope of use of these therapies is quite narrow and they also raise safety issues for patients. These are some of the reasons why ATMPs are extremely expensive and why they do not fit in the current regulatory and economic framework. If we want as many patients as possible to benefit from these medicines, we need to set a fair price for health insurance systems. On the basis of the Managed Entry Agreements (MEAs), the parties can negotiate on the performance of the product instead of signing a classic contract. The OECD distinguishes between two main types of agreements: financial and performance-based MEAs. Focusing on the latter, this paper will highlight its potential to facilitate access to ATMPs. The “coverage with evidence development (CED) contracts” allow treatment to be temporarily covered by the payer while a study evaluates its performance. Based on the results, coverage can be continued, withdrawn or extended, or prices are adjusted. The “pay-for-results contract” considers the uncertainty of results and organizes a “satisfied or reimbursed” policy. Here, the risk of innovation seems to lie with the laboratory and not with the community. Unfortunately, confidentiality is a barrier to evaluating objectively the strengths and weaknesses of these agreements. Greater transparency and an extended collaboration between States could help them negotiate better with drug laboratories.

# Contracts for better access to Advanced Therapy Medicinal Products

Blanka BARTOS<sup>1</sup>

<sup>1</sup> PhD Student in law, CREDIMI, University of Burgundy, Dijon, 27877, France.

**Acknowledgments:** This work has been supported by ANR-funded I-BioLex project (ANR-20-CE26-0007-01, coord. A. Mahalatchimy), by the Labex LipSTIC (ANR-11-LABX-0021), the Region Bourgogne - Franche Comté and the FEDER.



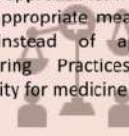
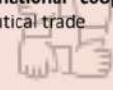
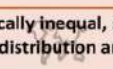
**Advanced Therapy Medicinal Products (ATMPs) Regulation (EC) No. 1394/2007**

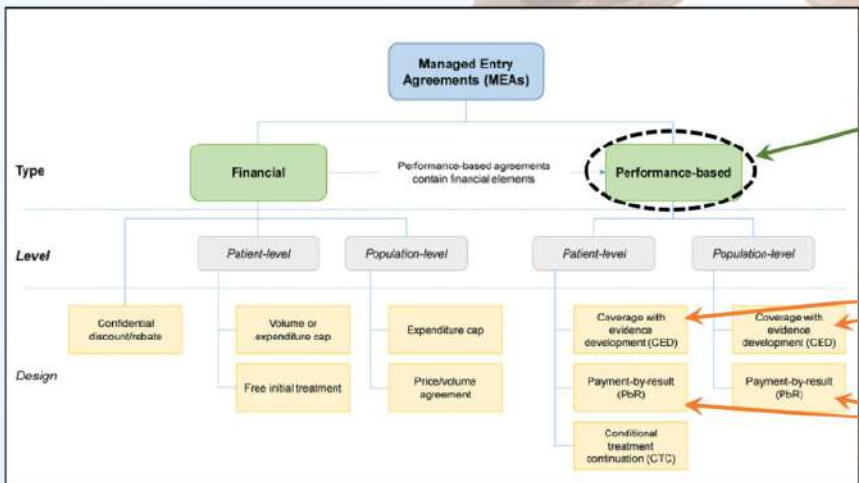
- Revolutionary treatments for serious diseases
- Target directly the cause
- Often one-shot treatments
- Expensive (1-2 million €) → Limited patient access

**Managed Entry Agreements (MEAs) are a possible solution**

- 'Risk-sharing agreements / arrangements between a manufacturer and a payer to enable access to a health technology (e.g.: ATMP) subject to specified conditions
- Address uncertainty about the performance of an ATMP or manage ATMP adoption to maximize their effective use or limit their budget impact
- Used mostly for orphan disease treatments as these medicines have high prices and also uncertainties on their long-term efficacy data

<b>Aim of the payers</b>	<b>Aim of the firms</b>
To provide patient access to new ATMPs quickly and at lower prices after marketing authorization	To sell the highest volume of ATMPs at the highest price

PROBLEMS	CONSEQUENCES
<b>High prices of ATMPs:</b> <ul style="list-style-type: none"> <li>› several years of development</li> <li>› high technicity</li> <li>› highly educated scientists</li> <li>› small number of patients (mostly with orphan diseases)</li> <li>› short period of treatment</li> </ul>	<b>Limited affordability</b> for patients and for States 
<b>High risks:</b> <ul style="list-style-type: none"> <li>› medical uncertainty</li> <li>› low number of patients, the laboratories cannot test the products on enough individuals to receive the market authorisation earlier</li> </ul>	<b>Delayed market entry</b> compared to other medicines 
<b>Heterogeneous types of ATMPs:</b> do not fit in the current regulatory and economic framework	<b>Risk-based approach</b> for manufacturers: choosing appropriate measures for each product instead of applying Good Manufacturing Practices → higher responsibility for medicine production 
<b>Lack of transparency</b> between Member States regarding price and efficiency of a new medicine	<b>Less international cooperation</b> , slower pharmaceutical trade 
<b>Complex fabrication and logistics of the distribution</b>	<b>Geographically inequal, slower and more expensive distribution and fabrication</b> 











More and more countries use this type of agreement with pharmaceutical companies to make sure to pay only for a treatment that works. However, 2/3 of EU States still use financial agreements.

**Coverage with evidence development:** fixed prices based on evidence of clinical trials and previous patient experiences

**Payment-by-result:** buyer pays only after those patients on whom the therapy worked

Source: Performance-based managed entry agreements for new medicines in OECD countries and EU member states, <https://www.oecd.org/fr/sante/systemes-sante/pharma-managed-entry-agreements.htm> (last seen: 03/10/2022)

PRESENT	FUTURE
<b>DIFFICULTIES of the application of performance-based agreements</b>	<b>GOOD PRACTICES of performance-based agreements</b>
 <b>Administrative burden</b> to collect data	 Used when benefit of <b>additional evidence</b> on product performance <b>outweighs the cost</b> of negotiating and executing other MEAs
 <b>Risk selection:</b> Payment-by-Result – the therapy would be given only to those patients on whom it is 100% successful	 Appropriate data sources and research designs to <b>address uncertainties</b>
 <b>High confidentiality</b> of all parts of the contracts	 <b>Transparency</b> assured by governance frameworks to allow payers to act upon additional evidences (e.g. exit or withdrawal the coverage)
 <b>Lack of transparency</b> of MEAs' process and content	 Minimum transparency level of MEAs' content and <b>limited confidentiality</b>

## Real access to ATMPs: the cost issue

**A. MAHALATCHIMY, A. DELAGE, L.-S. GILBERT, H.-Y. KUO, V. ROBY, C. CHABANNON**, Real access to ATMPs: the cost issue, ESGCT 2024, 22-25 October 2024, Roma, Italy (POSTER available at <https://shs.hal.science/halshs-04842702v1>)

### Abstract

While industry developed and manufactured Advanced Therapy Medicinal Products (ATMPs) benefit from a centralised marketing authorisation procedure that allows commercialization in all Member States of the European Union (EU), and despite improvement in EU citizen access to ATMPs being stated as one of the two major objectives when the ATMP regulation was released, actual patient access to ATMPs remains one of the most challenging issues to be addressed. Prices of ATMPs are among the highest despite difficulties in proving long term efficacy on significant numbers of patients, although it is fair to acknowledge that cumulative costs of supportive and curative treatments that are administered on repeated occasions may fall in the same ranges. Publicly accessible data show prices that vary from several hundreds of thousands euros to several million euros per treatment, with a continuous trend in increasing prices that has fuelled the concept of “financial toxicity” for those and other categories of treatments. Payment and reimbursement mechanisms as well as decisions on the levels of healthcare expenditures are established at national and possibly in some countries at regional levels by Healthcare Technology Assessment (HTA) agencies and other governmental bodies, with limited possibilities at the European level. Indeed, mainly apart from the Transparency directive and the recently strengthened collaboration in the field of HTA thanks to the adoption of the HTA regulation following the HTA initiatives at the EU level, each Member States is sovereign in determining its health expenses, including to decide on the reimbursement of ATMPs by its National health insurance system. Actual prices paid by public or private payers are not public, and a significant rebate may result from prior and mutual negotiations between drug manufacturers and healthcare providers, the latter receiving reimbursement from health insurers. In addition, specific programs such as the “Early Access” (“Accès précoces”) program in France may speed up access to innovative treatments in some countries, thus favouring a category of EU citizens over others. Thus, actual patient access to ATMPs in the European Union is not only limited, but also heterogeneous, highlighting the existing gap between the intentions stated in the ATMP Regulation and other EU documents and the actual achievements; these diverse factors resulting in an unsatisfactory situation where patients in need of lifesaving treatments face a shortage on a day-to-day basis, not because of insufficient manufacturing capacities as is the case for low-cost drugs, but because of insufficient payment capacities. This poster first provides an overview of the known prices of the 26 ATMPs that have so far obtained a marketing authorisation in the EU. It also highlights what is regulated at the EU and at the National levels in this area. Finally, it suggests potential solutions to improve patients’ access to ATMPs.



I-BIOLEX



CERIC





**V**

**Orphan Medicines**

## Improving access to innovative medicines: proposals from national authorities to revise the European legislation

**A. MAHALATCHIMY, F. LANSON, B. BARTOS, F. TABOULET**, Improving access to innovative medicines: proposals from national authorities to revise the European legislation, European Society for Gene & Cell Therapy Congress 2022, Edinburgh, the UK, 11-14 October 2022 (POSTER available at <https://shs.hal.science/halshs-03901248v1>); Abstract published in Human Gene Therapy, Volume: 33 Issue 23-24: December 14, 2022, A1-A212. <http://doi.org/10.1089/hum.2022.29225.abstracts>

### Abstract

Gene and cell therapies are currently considered as the main drivers of innovation in the treatment of genetic diseases and cancer therapies. They offer new hopes to rare disease patients as 80% of rare diseases are of genetic origin in the European Union. Hence, many gene and cell therapies have obtained the orphan medicine status under European regulation (EC) n° 141/2000, which provides incentives to promote the development of orphan medicines. The European Union tries to find a balance between the interests of industry, which should be encouraged to invest, patients' access to medicines, and the sustainability of health systems. Nevertheless, the current legal regime needs adaptation. Thus, the European Commission launched two public consultations in 2021: a first one specifically on the revision of the orphan medicines legislation, and then, another one on the revision of the general pharmaceutical legislation. Out of the 303 and 478 answers received, 12 and 30 respectively came from national authorities. On the basis of an analysis of their answers, this poster will discuss the criteria for orphan designation (e.g., the significant benefit which needs clarification and modification), as well as the incentives implemented, and patient access. It will highlight several proposals emphasized by national authorities that might be retained in the future legislations: to reward mainly truly innovative medicines, a transparency obligation on R&D costs before granting incentives to sponsors, or an obligation to launch the medicine in most Member States.

# IMPROVING ACCESS TO INNOVATIVE MEDICINES: PROPOSALS FROM NATIONAL AUTHORITIES TO REVISE THE EUROPEAN LEGISLATION

Aurélie Mahalatchimy<sup>[1]</sup>, Florence Lanson<sup>[2]</sup>, Blanka Bartos<sup>[3]</sup>, Florence Taboulet<sup>[4]</sup>

[1] Permanent Researcher in law at the French National Centre for Scientific Research (CNRS, research fellow), Law Faculty, UMR 7318 International, Comparative and European law (DICE) CERIC, CNRS, Aix Marseille University, Toulon University, Pau & Pays de l'Adour University, Aix-en-Provence, 13628, France. ; [2] CERPOP (Center for Epidemiology and Research in POPulation health), UMR 1295 Inserm, University of Paul Sabatier- Toulouse 3, Toulouse, 31062, France. ; [3] PhD Student in law, CREDIMI, University of Burgundy, Dijon, 27877, France. ; [4] Professor in Pharmaceutical Law and Health Economics, CERPOP, UMR 1295 Inserm, University of Paul Sabatier- Toulouse 3, Toulouse, 31062, France. **Acknowledgement:** This work has been supported by ANR-funded I-BioLex project (ANR-20-CE26-0007-01, coord. A. Mahalatchimy).

80% of rare diseases are of genetic origin in the EU

= Many advanced therapies have obtained the orphan medicine status under

**European regulation (EC) n° 141/2000 of 16 December 1999 on orphan medicinal products**

Provides orphan designation and incentives (market exclusivity for 10 years)

Needs to be revised. Why?

- Ensure the relevance of incentives granted to industry (to avoid abuses)
- Reward risk-taking and innovation more
- Improve equitable patient access in the EU

**Public consultations on revision of European legislation**

Orphan medicines legislation	General pharmaceutical legislation
7 May - 30 July 2021	28 Sept. - 21 Dec. 2021
303 answers including 12 public authorities from 9 Member States*	478 answers including 31 public authorities from 15 Member States**

\*AT, DE, DK, ES, FI, FR, HU, NL, SE ; \*\*AT, BE, CZ, DE, DK, EE, ES, FI, FR, HU, IS, MT, NL, PT, SE

## MAIN PROPOSALS FROM NATIONAL AUTHORITIES

*On the criteria for orphan designation*

*On the incentives granted to sponsors*

**Prevalence** : < 5 in 10,000 persons in the EU

- To be adjusted to avoid "salami slicing" (segmenting therapeutic indications)
- To be taken into account with the severity of the disease (**level of unmet medical need - UMN**)

**Significant benefit** : no EU satisfactory method of diagnosis, prevention or treatment, or drug significant benefit

- To be clarified and **graduated**

- **Proportionate to the level of UMN** (e.g. variable duration of market exclusivity)
- Focused on neglected therapeutic areas
- Conditional to certain obligations
  - Be transparent on R&D costs and actual prices
  - Launch in all or most Member States
  - UMN re-evaluated after commercialization
- Use experiences developed from covid-19 crisis
  - Joint procurement
  - Flexibility in clinical trials conduct

## DISCUSSION AND CONCLUSION

- Many isolated proposals : difficult to identify a consensus among the authorities
- Request of better cooperation between all agencies and more EMA support
- BUT emphasis on respecting the EU and Member States competences sharing

**Objectives to be balanced**

> Orphan single status transformed into a mosaic of statuses  
↳ Complexities : how to quantify ? which indicators ?

> Future EU considerations of national authorities proposals and answers from other respondents ?



## The current revision of the orphan medicinal products regulation in the European Union: what is at stake for gene and cell therapy?

**A. MAHALATCHIMY, E. GENNET,** The current revision of the orphan medicinal products regulation in the European Union: what is at stake for gene and cell therapy?, European Society for Gene & Cell Therapy Congress 2022, Edinburgh, the UK, 11-14 October 2022 (POSTER available at <https://shs.hal.science/halshs-03901429v1>); Abstract published in Human Gene Therapy, Volume: 33 Issue 23-24: December 14, 2022, A1-A212. <http://doi.org/10.1089/hum.2022.29225.abstracts>

### Abstract

In the European Union, gene and cell therapy medicinal products are mainly regulated by the specific legal framework applicable to Advanced Therapy Medicinal Products (ATMPs): regulation (EC) n°1394/2007. Yet most ATMPs that have been authorised for marketing in the European Union are also classified as orphan medicinal products. The latter are regulated by a different but also specific legal instrument : Regulation (EC) n°141/2000, which aims to promote the development of innovative medicines for orphan diseases thanks to a set of incentives for investigators. However, after twenty years of implementation, results are still unsatisfactory for several reasons. One of these reasons is that the market of orphan medicinal products had “started to look more similar to ‘standard’ medicines” than innovative medicines like ATMPs. Moreover, it has also been observed that even when marketed, orphan medicinal products fail in being equally accessible to patients in the different Member States. The European Commission has started a long and thorough revision process of the pharmaceutical legislation in order to give a new impulse to the development of, and access to, truly innovative orphan medicinal products, which may have a positive impact for patients as well as for investigators working on gene and cell therapies. In this poster, we will discuss what aspects of the revision of the regulation on orphan medicinal products may have an impact on the development of gene and cell therapy in the European Union.

# The current revision of the orphan medicines regulation in the EU: what is at stake for gene and cell therapy?

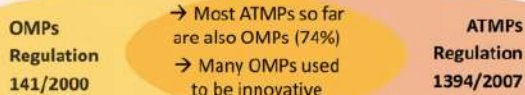
Aurélien Mahalatchimy<sup>1</sup> and Éloïse Gennet<sup>2</sup>

<sup>1</sup> Permanent Researcher in law at the French National Centre for Scientific Research (CNRS, CR), Law Faculty, UMR 7318 DICE CERIC, CNRS, Aix-Marseille University, Toulon University, Aix-en-Provence, France; <sup>2</sup> Post-doctoral Researcher in Law, Law Faculty, UMR 7318 International, Comparative and European laws (DICE) CERIC, CNRS, Aix-Marseille University, Toulon University, Aix-en-Provence, France.

**Acknowledgment:** This work has been supported by ANR-funded I-BioLex project (ANR-20-CE26-0007-01, coord. A. Mahalatchimy).

## REGULATORY CONTEXT

In the European Union, gene and cell therapy medicinal products are mainly regulated by the specific legal framework applicable to Advanced Therapy Medicinal Products (ATMPs) Regulation n°1394/2007; but also possibly by the Orphan Medicines (OMPs) Regulation n°141/2000.



## CURRENT INCENTIVES

EU Law, especially Regulation 141/2000 and Regulation 1394/2007, aims to incentivize the development and marketing of OMPs and ATMPs to palliate acute scientific and financial difficulties that these medicines represent.

Incentives for OMPs	Incentives for ATMPs (except hospital exemption)
Research funding for instance the E-RARE project, the European Joint Programme on Rare Diseases	Research funding for instance with the Joint undertaking on Innovative Medicines Initiative
Free scientific assistance from the European Medicines Agency and its Committee on Orphan Medicinal Products (COMP)	Fee reduction on scientific assistance from the European Medicines Agency and its Committee on Advanced Therapies (CAT)
Partially or totally reduced administrative fees for the marketing authorisation application process	Partially reduced administrative fees for the marketing authorisation application process
Mandatory centralized procedure for marketing authorization, valid in all EU Member States	Mandatory centralized procedure for marketing authorization, valid in all EU Member States
Ten-year commercial exclusivity	

## CHALLENGES AND ACTION PLAN

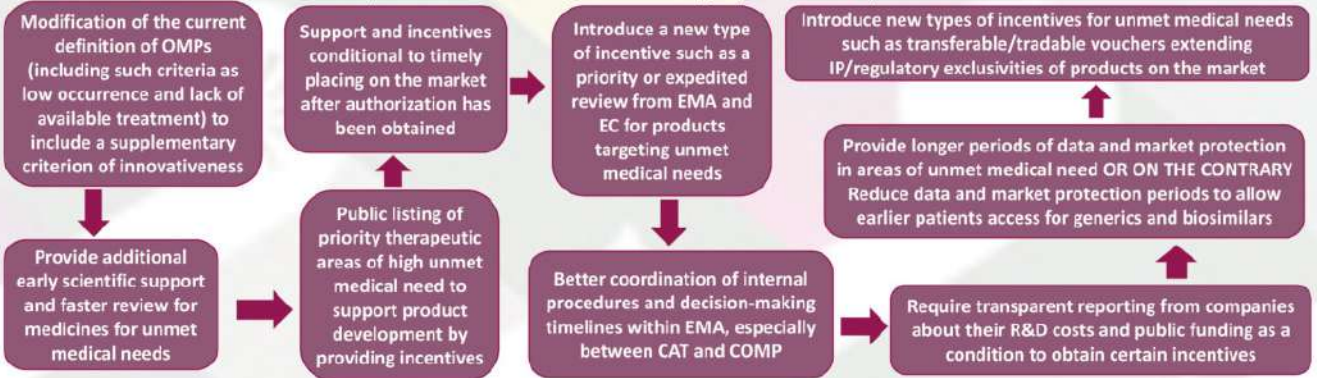
After 20 years of OMPs Regulation's implementation, results remain unsatisfactory. OMPs & ATMPs still fail in being equally accessible to patients in all Member States: e.g. their price and reimbursement level may vary between countries, or they are not even commercialized in others. Plus, OMPs look increasingly similar to standard medicines rather than innovative medicines like ATMPs (personalised and genetic medicine allow to isolate sublevels of one same condition for product to be qualified as OMP and benefit from incentives).

Fields of EU legislative action:



## POTENTIAL REGULATORY EVOLUTIONS

The European Commission has issued reports and conducted several public consultations from which potential solutions have emerged in order to enhance the promotion of innovative/advanced therapy orphan medicinal products:



## Some proposed new incentives are challenging:

**Priority review:** already tight timelines pressuring regulators

**Tradable exclusivity vouchers:** hindered timely access to market for generics and biosimilars for the most expensive products; unfair for patients by delaying lower prices of more used medicines; increased healthcare systems expenditures; increased uncertainty and litigation regarding IP/regulatory exclusivities

## CONCLUSION

Nevertheless, the revision of OMP regulation has the potential to provide solutions to address unmet medical needs of rare disease patients and greatly enhance innovation, and as such to be beneficial for ATMPs development:

- Focus on unmet medical needs that should be defined dynamically, ie taking into account the evolving scientific and medical context, in a multi-stakeholder setting;
- Dedicated public funding and financial incentives to promote research on unmet medical needs and neglected illnesses, health conditions, and populations;
- To introduce a corrective mechanism to prevent unaffordable prices or excessive return on investment: e.g. developer to justify the proposed price would be particularly relevant for high manufacturing costs of ATMPs.

The proposal for a new pharmaceutical legislation, including the revision of the OMP regulation, should be published by the European Commission by the end of 2022. The Council of the EU and the European Parliament will then try to reach an agreement and adopt a (usually amended) legislative act.



### REFERENCES

Regulation No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, OJ L 18, 22.1.2000, p. 1–5.  
 Regulation 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 No 726/2004, OJ L 324, 10.12.2007, p. 121–137.  
 European Commission, Joint evaluation of Regulation (EC) No 1501/2006 and Regulation No 141/2000, Brussels, 11.8.2020, SWD(2020) 163 final.  
 European Parliament resolution of 2 March 2017 on EU options for improving access to medicines (2016/2057(INI)).  
 European Commission, "Rare diseases. A major unmet medical need", 2017.  
 Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions, European Commission, Revision of the EU general pharmaceutical legislation - Pharmaceutical strategy for Europe, COM/2020/761 final.  
 European Parliament resolution of 24 November 2021 on a pharmaceutical strategy for Europe (2021/2013(INI)).  
 European Commission, Revision of the Union legislation on medicines for children and rare diseases - Public consultation factual summary report, 4 November 2021.  
 European Commission, Revision of the EU general pharmaceutical legislation - Public consultation factual summary report, 30 February 2022.



**VI**

**Actors**

## Which actors to influence the adoption of EU guidelines for Advanced Therapy Medicinal Products?

**A. MAHALATCHIMY, V. BRUNEL**, Which actors to influence the adoption of EU guidelines for Advanced Therapy Medicinal Products? International Society for Cell & Gene Therapy 2023 Paris Annual Meeting, Paris, France, 31 May- 3 June 3 2023 (POSTER available at <https://shs.hal.science/halshs-04290558v1>); Abstract published in Cytotherapy Volume 25, Issue 6, Supplement, May 2023, Page S161. [https://doi.org/10.1016/S1465-3249\(23\)00435-8](https://doi.org/10.1016/S1465-3249(23)00435-8)

### Abstract

Genes, cells, and tissues based medicinal products are specifically regulated as Advanced Therapy Medicinal Products (ATMPs) within the European Union (EU) from the adoption of Regulation (EC) n°1394/2007 on ATMPs. Beyond legislative requirements, the complexity and scientific technicity of these medicines, as well as the necessary flexibility to take into account the evolutions and the scientific and regulatory experience gained has led to the development of an important amount of guidelines in the field. These guidelines have mainly been adopted by the European Medicines Agency (EMA), the European regulatory agency especially in charge of the scientific assessment of medicines to be commercialized in the EU. Some of them have also been adopted by the European Commission which grants the final marketing authorization for medicines to enter the EU market. The adoption of EU guidelines involves a public consultation procedure to gather comments from stakeholders and interested parties. Our poster aims at mapping these different actors, and their potential changes over time, to allow for a realistic and concrete portrait of all stakeholders and interested parties involved in the field of ATMPs regarding their European regulation through guidelines. The identification of EU scientific guidelines applicable to ATMPs, and of the actors involved in the consultation process has led to the establishment of a database with over 200 organizations corresponding to fourteen guidelines for which dates of production range from 2008 to 2022. The organizations have been classified by type (Business, Academia, National bodies, etc.), country, and theme of the drafts of guidelines they commented on. This poster especially highlights and discusses which organizations have influenced the adoption of EU scientific guidelines on ATMPs; some of them commenting almost all guidelines in the field while others considered only certain guidelines. Findings concern both the number and quality of stakeholders with the aim to understand over time, what types of organizations from which country have been the most active in answering to guidelines' consultations, who were the major or more prolific respondents, and what themes were more often commented.

# WHICH ACTORS TO INFLUENCE THE ADOPTION OF EU GUIDELINES FOR ADVANCED THERAPY MEDICINAL PRODUCTS?

**Aurélien Mahalatchy:** Permanent Researcher in law at the French National Centre for Scientific Research (CNRS, chargée de recherche), Law Faculty, UMR 7318 International, Comparative and European laws (DICE) CERIC, CNRS, Aix-Marseille Univ, Toulon University, Pau & Pays de l'Adour University, Aix-en-Provence, France; Coordinator of I-Biolex project; Deputy coordinator and WP4 leader of EuroGCT project.

**Valentin Brunel:** Research Engineer, CNRS, UMR 7318 International, Comparative and European laws (DICE) CERIC, CNRS, Aix-Marseille Univ, Toulon University, Pau & Pays de l'Adour University, Aix-en-Provence, France

## Background and Methodology

Genes, cells, and tissues based medicinal products are specifically regulated as Advanced Therapy Medicinal Products (ATMPs) within the European Union (EU) from the adoption of Regulation (EC) n°1394/2007 on ATMPs. Beyond legislative requirements, the complexity and scientific technicality of these medicines, as well as the necessary flexibility to take into account the evolutions and the scientific and regulatory experience gained has led to the development of an important amount of guidelines in the field. These guidelines have mainly been adopted by the European Medicines Agency (EMA), the European regulatory agency especially in charge of the scientific assessment of medicines to be commercialised in the EU. Some of them have also been adopted by the European Commission (EC) which notably grants the final marketing authorization for ATMPs on the basis of EMA's assessment to enter the EU market. The adoption of EU guidelines involves a public consultation procedure to gather comments from stakeholders and interested parties.

These comments are then considered to establish the final version of the guidelines to be adopted to be used as reference documents in the field.

Who are these actors influencing the adoption of EU guidelines for Advanced Therapy Medicinal Products?

Our research team searched both the EMA and EC websites in order to identify all guidance documents specific to ATMPs. This led to the establishment of a list of 57 documents, among which 27 guidelines. This poster is dedicated to guidelines only.

Out of all 27 applicable guidelines identified, we considered only those for which a consultation process report was available. For older guidelines, sometimes no consultation was organized, and sometimes the subsequent report was not available on the EMA website.

Once all guidelines and associated reports on public consultation were collected, we identified all the actors involved in the consultation process: this led to the establishment of a database with 195 contributions from 147 organisations corresponding to thirteen guidelines for which dates of production range from 2006 to 2022.

For every guideline, we collected its title, date of publication, as well as the type of therapy to which it referred (either Advanced Therapy Medicinal Products (ATMPs) generally, Medicinal products based on Genetically Modified Organisms (GMO MP), Cell Therapy and Tissue Engineering Products (CT and TEP), or Gene Therapy Medicinal Products (GTMP)).

For each guideline, all organisations participating in the public consultation process were indexed and sorted in a table. Additional information was collected on the organisations' websites, regarding their typology, country of registration and specific activity.

The typology of organisations was constructed using all information available to sort out organisations to clearly identify the main polarizations between them.

## Main figures

Table 1: Numbers of organisations involved in different types of guidelines

Guideline	Author	Theme	Date	Number of orgs
Non-clinical testing for inadvertent germline transmission of gene transfer vectors	EMA	GTMP	16/11/2006	4
Environmental risk assessments for medicinal products containing, or consisting of, genetically modified organisms (GMOs)	EMA	GMO MP	11/12/2006	4
Human cell-based medicinal products	EMA	CT and TEP	21/05/2008	20
Non-clinical studies required before first clinical use of gene therapy medicinal products	EMA	GTMP	30/05/2008	4
Scientific requirements for the environmental risk assessment of gene-therapy medicinal products	EMA	GTMP	30/05/2008	7
Follow-up of patients administered with gene therapy medicinal products	EMA	GTMP	22/10/2009	1
Guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products	EMA	ATMPs	15/10/2010	6
Potency testing of cell-based immunotherapy medicinal products for the treatment of cancer	EMA	GTMP	21/07/2016	4
Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products	EC	ATMPs	25/11/2017	55
Quality, preclinical and clinical aspects of gene therapy medicinal products	EMA	GTMP	22/05/2018	29
Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal Products	EC	ATMPs	10/10/2019	34
Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells	EMA	GMO MP	12/11/2020	20
Guideline on core SmPC, Labelling and Package Leaflet for advanced therapy medicinal products (ATMPs) containing genetically modified cells	EMA	ATMPs	10/05/2022	9

## Results

- 11/13 guidelines have been adopted from 2008.
- 11/13 guidelines have been established by EMA while 2/13 guidelines have been established by EC.
- 4/13 guidelines relate to ATMPs in general.

- 6/13 guidelines relate to GTMP.
- 2/13 guidelines relate to GMO MP.
- 1/13 guideline relate to CT & TEP.

## Discussion

There is a wide scale of involvement in public consultation processes, ranging from only 1 to 55 organisations having been involved. The number of organisations involved in public consultations processes is linked to the guidelines' topics and not to a potential increase due to better awareness of the process with time.

Almost half of the guidelines for which a report on public consultation is available, have been adopted in the field of GTMP which highlights the rise of this type of ATMPs as well as the particular need for regulatory guidance for their development and commercialisation in the EU. On the opposite, only one guideline covers CT & TEP together.

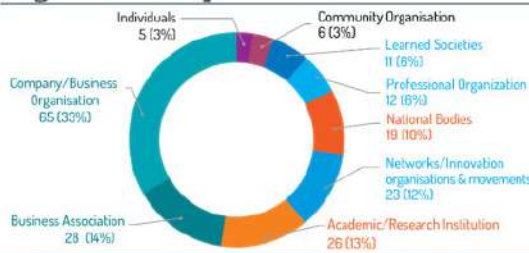
The guidelines which involved the highest number of organisations during the public consultation processes are the ones adopted by the EC. This can be explained

by both their highest legal value and the wider scope of their topic on particularly challenging aspects of ATMPs development: Good Manufacturing Practice and Good Clinical Practice specific to ATMPs.

The other guidelines involving a high number of organisations during the public consultation processes relates to wide scientific aspects of the main types of ATMPs: Quality, preclinical and clinical aspects of gene therapy medicinal products for GTMP (29), Human cell-based medicinal products for CT & TEP (20) and Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells for GMO MP (20). Here also, the guideline on GTMP has involved more participation than for other types of products. Guidelines on CT & TEP and on GMO MP have involved the same number of organisations, even though only the first one covers two sub-categories of ATMPs explicitly defined at the legislative level (Regulation (EC) n°1394/2007 and Directive 2009/120/EC).

The other guidelines involving less organisations (9 maximum) relate to various types of ATMPs, or ATMPs generally and they cover very particular scientific (e.g., potency testing) or regulatory (e.g., packaging & labelling) aspects of their development, or specific procedure (e.g., certification).

## Organisations' profile

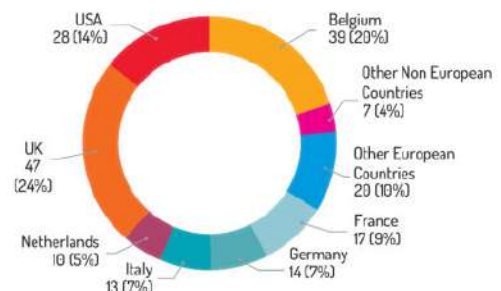


Graph 1: Typology of organisations involved in the consultation processes of ATMPs guidelines.

**Discussion:** The countries most represented are the most active in the development of ATMP: UK, Belgium, USA, France, Germany, Italy and the Netherlands. Nevertheless, the important involvement of Belgium (20%) should be put in perspective with the European institutions being mainly established in Brussels, which leads to an important amount of organisations having their headquarters there.

The important involvement of the UK (24%) can be explained by the UK being one of the leading countries in the field, although almost all public consultations processes considered (12/13) occurred before Brexit. Thus, such main position of the UK may change in the future. The important involvement of the USA (14%) can be astonishing given that the public consultations relate to European regulation. However, it reveals how much the field is international and how much the European Market is targeted by external countries, especially the USA.

**Discussion:** Companies and business associations account for almost half of all contributions (47%). Community organisations (3%) and individuals (2%), on the contrary, seldom contribute. As for public sector organisations, such as national bodies and academic institutions, they hold the middle ground (24%). These results can be explained by the availability of means (human and financial ones in particular regarding necessary time and knowledge) to contribute to the process of public consultation.



Graph 2: Organisations involved in the consultation processes of ATMPs guidelines by country.

## Most contributing organisations

Table 2a: Organisations by number of contributions

Number of contributions	Organisations
Three or more	9
Two	25
One	115

Out of the 9 organisations which have contributed to 3 or more guidelines:

- 4/9 are located in Belgium.
- 4/9 are Business Associations
- 5/9 are from the private sector (Company or Business Association).
- 2/9 are Networks/Innovation Organisations.

Table 2b: Name, type and country of organisations answering to 3 or more guidelines

Organisation	Type	Country	Number of contributions
European Federation of Pharmaceutical Industries and Associations (EFPIA)	Business Association	Belgium	6
European Association for Biomedicine (EunimBio)	Business Association	Belgium	5
Alliance for Regenerative Medicine (ARM)	Networks/Innovation Organisation	USA	4
Cell and Gene Therapy Catapult	Networks/Innovation Organisation	UK	4
European Association of Hospital Pharmacists (EAHP)	Professional Organisation	Belgium	4
European Biopharmaceutical Enterprises (EBE)	Business Association	Belgium	4
International Society for Cell & Gene Therapy (ISCT)	Learned Society	Canada	4
German Pharmaceutical Industry Association (BPI eV)	Business Association	Germany	5
Vain Consulting Life Sciences (VCLS)	Company/Business Organisation	France	5

## Discussion

As long as only few organisations have contributed to 2 and to 3 or more consultations, and 78,2% of organisations contribute only once to a consultation process on ATMPs guidelines, it appears the contribution are based on the topics of the guidelines rather than on an habit to be involved in this process.

Among organisations contributing most often, the private sector is leader given the means it can dedicate to this activity; and Belgium is the most represented country given the strategic position of being in Brussels to know and influence EU policy and regulation. Surprisingly, the public sector, mainly represented by National bodies and academic/ research institution, does not appear among the organisations contributing the most often to public consultation regarding ATMPs guidelines. It implies a participation based on the topics of the guidelines rather than an habit. Although this can be understood for academic/ research institution which generally focus on specific area of research even in the delimited field of ATMP, it is more questionable for national bodies, and especially national authorities, such as national medicines agencies, which could have been considered as the main contact point for ATMP developers, despite main EMA competences, given national languages and their potential interface's role between the EMA and ATMPs developers located in National EU Member States.

## General conclusion

- Most guidelines have been adopted after the adoption of Regulation (EC) n°1394/2007 on 13 November 2007 and have contributed to its practical implementation.
- Most guidelines applicable to ATMPs have been established by the EMA. It highlights both the main role of the agency in this field and the technical specificity of ATMPs. Guidelines on Good Manufacturing Practice and on Good Clinical Practice specific to ATMPs have been adopted by the EC in accordance with the provisions of Regulation (EC) n°1394/2007.
- More EMA guidelines but more contributions on EC guidelines due to highest legal value and wider scope of their topic on particularly challenging aspects of ATMPs development
- A wide scale of involvement in the public consultation processes: from 1 to 55 organisations
- The more general a guideline is, the more contributions it obtains
- Involvement in the public consultations processes is linked to the guidelines' topics, and neither to a potential increase due to better awareness of the process on time nor to an habit to contribute even for national regulators.

- GTMP is the category of ATMPs raising the most of interest
- The private sector is leader in answering public consultation on ATMPs guidelines, both regarding the overall amount of contributions and the organisations that contributed the most often.
- The countries most represented are the UK, Belgium, USA, France, Germany, Italy and the Netherlands
- The major involvement of the UK may change in the future following Brexit.
- The important involvement of the USA reveals how much the field is international and how much the European Market is targeted by external countries, especially the USA.
- The important involvement of Belgium should be put in perspective with the European institutions being mainly established in Brussels which leads to an important amount of organisations having their headquarters there and to organisations that may be more used to EU policy and regulation (Belgium is the most represented country among the organisations contributing most often).

## Comparing actors participating in the adoption process of SoHO and ATMP regulations at the European level

V. BRUNEL, A. MAHALATCHIMY, Comparing actors participating in the adoption process of SoHO and ATMP regulations at the European level, European Society for Gene & Cell Therapy Congress 2023, Brussels, Belgium, 24-27 October 2023 (POSTER available at <https://shs.hal.science/halshs-04290588v1>)

### Abstract

Genes, cells, and tissues based medicinal products are regulated as Advanced Therapy Medicinal Products (ATMPs) within the European Union (EU). Nevertheless, the very first steps of development of ATMPs, i.e. donation, procurement and testing of human cells and tissues, are governed by the tissues and cells Directive. The latter is being revised and the European Commission has adopted a proposal for a new regulation covering Substances of Human Origin (SoHO) more widely. Both the regulation on ATMPs and the current proposal for a regulation on SoHO, as EU legislative acts, have involved a public consultation procedure to gather comments from stakeholders and interested parties. How similar or different are the actors that influence the framing of EU legislation applicable to gene and cell therapy?

Our poster aims at mapping these actors for both ATMPs and SoHO, and their potential changes over time, to identify possible differences and/or convergences as to who exactly has been involved in ATMPs and SoHO regulations.

The identification of answers to the relevant public consultation procedures has led to the establishment of a database with 530 contributions corresponding to both ATMPs and SoHO regulations' documents. The participating organisations have been classified by type (Business, Academia, National bodies, etc.) and country according to the documents they commented on.

Findings concern firstly the main differences between SoHO and ATMPs regarding participating organisations. Secondly, some organisations also revealed themselves as particularly active in both areas of ATMPs and SoHO, which highlights their interest for the entire development cycle of ATMPs and its related legislation.

Contrasting the repartition of stakeholders interested in ATMPs and SoHO may indeed explain some of the differences in the way the regulation is being constructed and its level of detail: the more a type of organisations is involved, the more it has a chance to impact the regulation's framing according to its own specific interest.s

## Comparing actors participating in the adoption process of SoHo and ATMP regulations at the European level

Aurélié Mahalatchimy (1), Valentin Brunel (2)

1 - Permanent Researcher in law at the French National Centre for Scientific Research (CNRS, CR), Law Faculty, UMR 7318 International, Comparative and European laws (DICE) CERIC, CNRS, Aix Marseille Univ., Toulon Univ., Pau & Pays de l'Adour Univ., Aix-en-Provence, France; Coordinator of I-BioLex project; Deputy coordinator and WP4 leader of EuroGCT project.

2 - CNRS Research Engineer, UMR 7318 DICE CERIC, CNRS, Aix Marseille Univ., Toulon Univ., Pau & Pays de l'Adour Univ., Aix-en-Provence, France. Contact: valentin.BRUNEL@univ-amu.fr

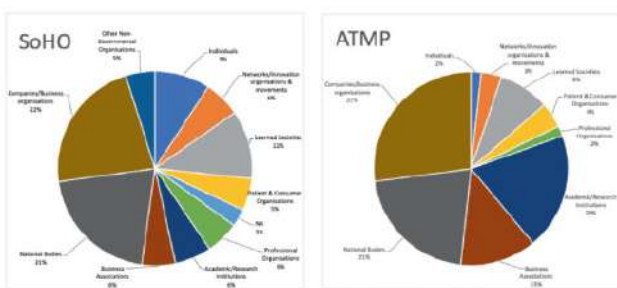
### INTRODUCTION

- Genes, cells, and tissues based medicinal products are regulated as Advanced Therapy Medicinal Products (ATMPs) within the European Union (EU). Nevertheless, the very first steps of development of ATMPs, i.e. donation, procurement and testing of human cells and tissues, are governed by the tissues and cells Directive. The latter is being revised and the European Commission has adopted a proposal for a new regulation covering Substances of Human Origin (SoHO) more widely. Both the regulation on ATMPs and the current proposal for a regulation on SoHO, as EU legislative acts, have involved a public consultation procedure to gather comments from stakeholders and interested parties. These comments are then taken into account to adapt the legislative frameworks.
- Legislation on SoHO apply to the first stage of developments of all ATMPs, and is also wider as it applies to the use of human origin substance for therapeutic purposes which are not ATMPs.
- Who are these actors influencing the adoption and evolution of EU regulation and legislative acts for Advanced Therapy Medicinal Products and are they different from those influencing the legislation on Substances of Human Origin?

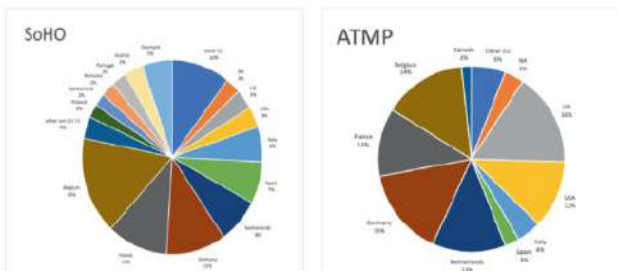
### METHODOLOGY AND CORPUS

- Our research team identified all consultations relative to legislative acts pertaining to both Substances of Human Origin (SoHO) and Advanced Therapy Medicinal Products (ATMPs). This led to the establishment of a list of 5 documents. Once all public consultations were collected, we identified all the actors involved in the consultation process: this led to the establishment of a database with 530 contributions from 352 organisations corresponding to the five public consultations.
- For every legislative act public consultation, we collected its title, date of publication, as well as the type of therapy to which it referred (either Advanced Therapy Medicinal Products (ATMPs) or SoHO).
- For each consultation, all organizations participating in the public consultation process were indexed and sorted in a table. Additional information was collected on the organisations' websites, regarding their typology, country of registration and specific activity.
- The typology of organizations was constructed using all information available in order to sort out organizations to clearly identify the main polarizations between them. For organizations participating in SoHO consultations, we had to change the classification already available on the EU website, since it was declarative and many contributors did not fill in the right category, according to our standards.

### FINDINGS : PROFILE OF PARTICIPATING ORGANISATIONS IN SoHO AND ATMPs



Figures 1, 2 : Types of participating organisations in SoHO and ATMP consultations



Figures 3, 4 : Countries of participating organisations in SoHO and ATMP consultations

#### Main similarities

- Companies/Business organisations = first most participating organisations in both SoHO (22%) and ATMP (27%) consultations
- National Bodies = second most and equally participating organisations in both SoHO and ATMP consultations (21%)
- Patients & Consumer Organisations have almost equally contributed to SoHO consultations (5%) and ATMP consultations (4%) and they are in sixth position in both cases.

#### Main differences

- Academic/Research institutions have very much (third position) participated in ATMP consultations (20%), almost equally to National Bodies, and contrary to SoHO consultations (6%).
- Business Associations have participated more in ATMP consultations (fourth position with 13%) than in SoHO consultations (shared fifth position with 6%).
- Individuals have far more participated in SoHO consultations (fourth position with 9%) than in ATMP consultations (shared last position with 2%).
- Professional Organisations, Academic/Research institutions, Business Associations, Networks/Innovation Organisations and movements have similarly participated in SoHO consultations (shared fifth position with 6%).
- Networks/Innovation Organisations & movements and Professional Organisations have participated twice as much in SoHO consultations (shared fifth position with 6%) as in ATMP consultations (respectively 3% and 2%).
- Organisations classified as "Other Non-Governmental organisations" and "NA" for "Not Available" information have participated in SoHO consultations (respectively 5% and 3%) and not in ATMP consultations.
- Learned Societies have slightly more contributed to SoHO consultations (11%) than to ATMP consultations (8%), but they appear in third position in the former and in fifth position only in the latter.

#### Main similarities

- With the exception of the UK and the USA, the countries that contributed the most to both SoHO and ATMP consultations are the same: Belgium, France, Germany, the Netherlands, Spain, and Italy.

#### Main differences

- The UK and USA were part of the countries contributing most to ATMP consultations (respectively 16% and 12%), but not to SoHO consultations (3% in both cases).
- More EU countries have contributed to SoHO consultations.
- Canada has clearly appeared as country participating in ATMPs consultations (2%) and not in SoHO consultations.
- France, Germany, and the Netherlands which were among the countries contributing most to SoHO consultations (with Belgium) participated slightly more to ATMP consultations.

### FINDINGS : ORGANISATIONS PARTICIPATING TO BOTH SoHO AND ATMPs CONSULTATIONS

Name of the organisation	Typology	Country	Name of the organisation	Typology	Country
Centre National de Traitement	National Bodies	Italy	European Society for Blood and Bone Marrow Transplantation (EBMT)	Learned Societies	Netherlands
Establishment Français de Sang	National Bodies	France	European Society for Human Reproduction (ESHRE)	Patients and Consumer Organisations	Belgium
EUROPE - European Confederation of Pharmaceutical Entrepreneurs	Business Associations	Belgium	Finland Blood Cross Blood Service	National Bodies	Finland
European Association for Bone Marrow (European)	Business Associations	Belgium	International Human Frontiers of Transplantation (IHFT)	Learned Societies	Netherlands
European Association of Clinical Pharmacists (EACP)	Professional Organisations	Belgium	Lelids University Medical Center	Academic/Research institutions	Netherlands
European Association of Tissue Banks (EATB)	Learned Societies	Denmark	Paul Ehrlich Institut Germany	National Bodies	Germany
European Eye Bank Association (EEBA)	Learned Societies	Italy	The Veneto Eye Bank Foundation (Fondazione Banca degli Occhi del Veneto - CBV)	Academic/Research institutions	Italy
European Federation of Pharmaceutical Industries and Associations (EFPIA)	Business Associations	Belgium	House Bank of France (HBF)	Companies/Business organisations	France
European Medicines Agency (EMA)	National Bodies	UK	Underlying Organized Forces	Academic/Research institutions	Belgium

- Only 18 organisations out of a total of 352 (AM1) identified organisations participated in both a SoHO and an ATMP consultations (5.1/AM2) %.
- Among them, regarding their typology:
  - National bodies (5/18, 27.8%) and Learned Societies (4/18, 22.2%) have been the most represented.
  - Academic/Research Institutions and Business associations holds the middle ground (3/18, 16.7% for each category).
  - Companies/Business Organisations, Patient and Consumer Organisations, and Professional Organisations have been the less represented (1/18, 5.6% each)
- Among them, regarding their countries:
  - Belgium has been the most represented (6/18, 33.3%), followed by Italy and Netherlands (3/18, 16.7% each), then France and Germany (2/18, 11.1% each), and finally Finland and the UK (1, 5.6% each). However, although the EMA counted for the UK for country's attribution purpose (as it was based there before Brexit), it is a European Union agency.
  - No Networks/Innovation organisations & movements, individuals, Other Non-Governmental organisations participated in both a SoHO and an ATMP consultations.

### Conclusions

- Comparing the types of organisations participating in SoHO & ATMPs consultations respectively
  - Companies/Business Organisations and National Bodies are the 2 types of organisations most participating in both SoHO and ATMP consultations.
  - National Bodies have highly and equally participated in both SoHO and ATMP consultations (21%).
  - ATMP consultations highlight a stronger participation of private organisations (27% of Companies/Business Organisations in first position and 13% of business associations in fourth position) and of Academic/research institutions (20%, third position) in addition to National bodies (21%, second position).
  - SoHO consultations highlight a stronger participation of Learned societies (11%, third position) and Individuals (9%, fourth position) in addition to Companies/Business Organisations (22%, first position) and National bodies (21%, second position).

#### Comparing the countries of organisations participating in SoHO & ATMPs consultations respectively

- Apart from the UK and the USA which contributed far more to ATMP consultations, the countries that contributed the most to both SoHO and ATMP consultations are the same. In descending order: Belgium, France, Germany, the Netherlands, Spain, and Italy.
- For the UK, Brexit occurred just before SoHO consultations and the UK was part of the EU during ATMP consultations.
- The important involvement of Belgium to both ATMP and SoHO consultations should be put in perspective with the European institutions being mainly established in Brussels, which leads to an important amount of organisations having their headquarters there.
- Leading European countries in the field of ATMP and use of SoHO for therapeutic purposes.
- The important involvement of the USA (12%) and the visible involvement of Canada (2%) in ATMP consultations can be astonishing given that the public consultations relate to European regulation. However, it reveals how much the ATMP field is international and how much the European Market is targeted by external countries, especially the USA.
- Contrary to the noticeable international dimension of ATMP consultations, the SoHO consultations have involved more EU countries.

#### Only few organisations participated to both a SoHO & an ATMP consultations

- Only 5% of the 352 identified organisations participated in both a SoHO and an ATMP consultations.
- The strongest participation of National bodies to both a SoHO and an ATMP consultations can be explained by their functions.
- Contrary to the analysis of organisations that answered to ATMP and SoHO separately (See figures 1 & 2), Business associations have been more active than single Companies/Business Organisations when contributing to both a SoHO and an ATMP consultations.
- The countries represented in the 18 organisations that participated in both a SoHO and an ATMP consultations correspond to the most active European countries in both fields, except for Spain and Finland (See figures 3 & 4).

## An exploratory analysis on the involvement of European organisations in the field of biomedical innovation

**A. SCHEER, V. BRUNEL, S. GUION, I. CHIV, M. MORELL, M. DURAND, O. JOANINA, V. ANDRIEU, A. MAHALATCHIMY**, An exploratory analysis on the involvement of European organisations in the field of biomedical innovation, European Society for Gene & Cell Therapy Congress 2023, Brussels, Belgium, 24-27 October 2023 (POSTER available at <https://shs.hal.science/halshs-04290569v1>)

### Abstract

Many actors influence the framing of EU legislation and regulation applicable to gene and cell therapy. Nevertheless, one can wonder how much their activity is focusing on gene and cell therapy or whether it is part of a wider set of activities taking place in the more general theme of biomedical innovation. From an identification of the actors involved in the public consultation process of adoption of Regulations on Advanced Therapy Medicinal Products, on substances of human origin, and of guidance applicable to ATMPs, a few of them have been selected in order to conduct more specific analysis. Our selection process for this pilot analysis included the following criteria: European level organisation, degree of the involvement in the above-mentioned consultation processes, combination between organisations the names of which imply either a very specific or a general remit. Another choice has been to include European organisations particularly relevant for pharmacists, as professionals involved all along the medicinal products' life cycle. It resulted in a set of 13 European organisations: 5 business associations (Medtech Europe, European Federation of Pharmaceutical Industries and Associations, European Biopharmaceutical Enterprises, European Associations for Bioindustries, European Confederation of Pharmaceutical Entrepreneurs), 2 professional organisations (European Industrial Pharmacists Group, European Association of Hospital Pharmacists), 4 learned societies (European Society of Gene and Cell Therapy, European Society for Blood and Bone Marrow Transplantation, European Eye Bank Association, European Association of Tissue Banks, European Association of Hospital Pharmacists), 1 research institution taking the form of European project (European Network for the Advancement of Clinical Gene Transfer & Therapy), 1 European network based on national medicines agencies (EU innovation network). Then, in depth research has been conducted on the website of each organisation in order to identify their activity within and beyond gene and cell therapy regarding biomedical innovation in general. On the one hand, this poster highlights the main results concerning their organization: especially structure, governance, potential change of name or merger over time, as well as specific or general working committees. On the second hand, their fields of activity are described following an analysis based on a set of keywords. Whereas some keywords are heavily used by all organisations (gene therapy, cell therapy for example), others are more specific (orphan medicine) and others very rare (organoid).



I-BIOLEX



UMR 7318  
Droit International,  
Composé et Européen



CERIC

# AN EXPLORATORY ANALYSIS ON THE INVOLVEMENT OF EUROPEAN ORGANISATIONS IN THE FIELD OF BIOMEDICAL INNOVATION

A. Scheer<sup>1</sup>, V. Brunel<sup>2</sup>, S. Guon<sup>3</sup>, I. Chiv<sup>3</sup>, M. Morell<sup>3</sup>, M. Durand<sup>3</sup>, O. Jacinà<sup>3</sup>, V. Andrieu<sup>4</sup>, A. Mahalatchimy<sup>5</sup>

<sup>1</sup> Pharmacy Resident, Marseille Public Hospital (AP-HM) and Faculty of Pharmacy, Aix-Marseille, France. <sup>2</sup> Research Engineer, CNRS, UMR 7318 International, Comparative and European Laws (DICE) CERIC, CNRS, Aix-Marseille University, Toulon University, Pau & Pays de l'Adour University, Aix-en-Provence, France. <sup>3</sup> Students in 4th year of Pharmaceutical Sciences, Industry and research track, Aix-Marseille University, France. <sup>4</sup> Senior lecturer in Industrial Pharmacy and Pharmaceutical Regulation, Faculty of Pharmacy, Aix-Marseille University, Research Unit Microbes Evolution Phylogeny and Infection (MEPHI) Aix-Marseille University, IRD, France. <sup>5</sup> Permanent Researcher in law at the French National Centre for Scientific Research (CNRS, CR), Law Faculty, UMR 7318 DICE CERIC, CNRS, Aix-Marseille University, Toulon University, Aix-en-Provence, France.

**Acknowledgements:** This work has been supported by the European Union's Horizon 2020 research and innovation programme under grant agreement No 965241 and by ANR-funded I-BioLex project (ANR-20-CE26-0007-01).

## INTRODUCTION AND METHODOLOGY

Many actors influence the framing of EU legislation and regulation applicable to gene and cell therapy. Nevertheless, one can wonder how much their activity is focusing on gene and cell therapy or whether it is part of a wider set of activities taking place in the more general theme of biomedical innovation. Biomedical innovation has been considered widely as a set of processes and products based on biological elements of human or animal origin intended to generate both improvement in health and economic competitiveness. From an identification of the actors involved in the public consultation process of adoption of European Regulation n°1394/2007 on Advanced Therapy Medicinal Products, of guidance applicable to ATMPs and adopted either by the European Medicines Agency or by the European Commission, and on the Proposal for a European Regulation on substances of human origin, and of guidance applicable to ATMPs, a few of them have been selected in order to conduct more specific analysis. Our selection process for this pilot analysis included the following criteria: European level organisation, degree of the involvement in the above-mentioned consultation processes, combination between organisations the names of which imply either a very specific or a general remit. Another choice has been to include European organisations particularly relevant for pharmacists, as professionals involved all along the medicinal products' life cycle. It resulted in a set of 13 European organisations including 3 business associations, 2 professional organisations, 4 learned societies, 1 research institution taking the form of European project, 1 European network based on national medicines agencies. Then, in-depth research has been conducted by pharmaceutical sciences students between January and April 2023 on the website of each organisation in order to identify their activity within and beyond gene and cell therapy regarding biomedical innovation in general. First, we analysed their structure, governance, typology and possible name changes or mergers over time. Second, we collected the occurrences of general and specific keywords relating to biomedical innovations both through an exploration of the tabs dedicated to their production and by using the "search" function when it exists on the websites of the organisations studied. Beyond "biomedical innovation" itself, the general keywords used were: therapeutic innovation, innovative medicine, regenerative medicine, biotechnology, advanced therapies, nanomedicine, organoid. The specific keywords used were: biological medicine, orphan medicine, advanced therapy medicinal products, gene therapy, cell therapy, tissue engineering, genome editing. This analysis is considered to be exploratory as a limited number of organisations has been studied from the interests of the pharmaceutical sciences students involved and the feasibility required a limited number of keywords to be searched for. Terms that are similar to our keywords may have been mentioned on the websites of the organisations studied although we have not searched for them. For instance, "genome editing" and "cell therapy" were searched for but not "gene editing" and "cellular therapy". Nevertheless, some of these similar keywords have been identified when they appeared in the names of working groups of the organisations studied.

## RESULTS

### Main elements of structure

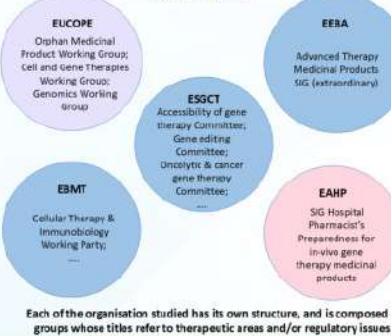
**Mergers among 2 business associations studied**  
MedTech Europe is a 2021 merger of EDMA and Eucomed.  
EPPIA & European Biopharmaceutical Enterprises (EBE) collaborated for a long time (common members, papers,...) until EBE has become a specialized group of EPPIA.

**Changes of names of 2 learned societies**  
Working Group on Human Gene Transfer and Therapy (EWGT) > 1998:  
European Society of Gene Therapy (ESGT) > 2007: European Society of Gene and Cell Therapy (ESGCT)  
European association of tissue banks (EATB) > 2016: European association of tissue and cell banks (EATCB)

### Reading grid

Not often/rarely (<25%)  
Slightly often (≥25%)  
Fairly often (50%)  
Very often (≥75%)  
Always (100%)

### Groups targeting biomedical innovations in the organisations studied in 2023



Each of the organisation studied has its own structure, and is composed of groups whose titles refer to therapeutic areas and/or regulatory issues.

### Type and date of creation of every organisation

ORGANISATION	TYPE	CREATION DATE
European Federation of Pharmaceutical Industries and Associations (EFPIA)	Business association	1978
The European Association for Bioindustries (Europabio)	Business association	1996
European Biopharmaceutical Enterprises (EBE)	Business association	2000
European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)	Business association	2008
MedTech Europe	Business association	2012
European association of tissue and cell banks (EATCB)	learned Society	1949
European group for Blood and Bone Marrow Transplantation (EBMT)	learned Society	1974
European Eye Bank Association (EEBA)	learned Society	1989
European Society of Gene and Cell Therapy (ESGCT)	learned Society	1992
European Industrial Pharmacists Group (EIPG)	Professional organisation	1966
European association of hospital pharmacist (EAHP)	Professional organisation	1969
European Network for the Advancement of Clinical Gene Transfer & Therapy (CLINIGENE)	Research Project	2006-2011
European Innovation Network (ENI)	European Network	2015

### Occurrences of general terms within the production of the organisations

	Biomedical innovation	Therapeutic innovation	Innovative medicine	Regenerative medicine	Biotechnology	Advanced therapies	Nanomedicine	Organoid
European Federation of Pharmaceutical Industries and Associations (EFPIA)	7%	4%	7%	7%	14%	14%	0%	0%
European Associations for Bioindustries (Europabio)	5%	5%	14%	32%	23%	45%	0%	0%
European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)	0%	0%	23%	14%	0%	23%	3%	0%
MedTech Europe	0%	0%	50%	50%	50%	50%	0%	0%
European association of tissue and cell banks (EATCB)	50%	75%	50%	75%	100%	75%	0%	50%
European Society for Blood and Marrow Transplantation (EBMT)	0%	8%	3%	9%	9%	20%	0%	0%
European Eye Bank Association (EEBA)	50%	30%	0%	50%	50%	50%	0%	0%
European Society of Gene and Cell Therapy (ESGCT)	0%	0%	9%	9%	0%	18%	0%	0%
European Industrial Pharmacists Group (EIPG)	0%	0%	50%	50%	50%	50%	0%	0%
European association of hospital pharmacist (EAHP)	50%	83%	50%	0%	50%	50%	0%	0%

### MAIN RESULTS

- ♦ **"Advanced therapies"** is the most used term. It is the only one that has been used by every organisations in our study, whatever their typology. However, its use has been quantitatively various ranging from not often/rarely (<25%) to very often (≥75%) without obvious result linking the quantity of use of this term to the type of organisation using it.
- ♦ **"Regenerative medicine"** and **"innovative medicine"** have been very used by the studied organisations (9 out of 10 in both cases). Nevertheless, the use of "innovative medicine" appears much more contrasted (being either not often/rarely or very often) than the use of "regenerative medicine" that appears all along our gradation scale of use.
- ♦ **"Biotechnology"** has also been very used (8 out of 10 organisations), its use has been less clearly contrasted than for "innovative medicine" but also slightly less gradated than for "regenerative medicine".
- ♦ **"Therapeutic innovation"** and **"biomedical innovation"** have been used respectively by 6/10 and 5/10 organisations. Their use has been quite equally contrasted (Not often or rarely used by half of the organisations and fairly often or more for the other half). However, contrary to "biomedical innovation", "therapeutic innovation" has been used very often by 2/3 of the organisations that used this term.
- ♦ **"Nanomedicine"** and **"organoid"** have been the less used terms. They are the only terms that have been mentioned only by one organisation (respectively <5% EUCOPE as a business association, and 50% EATCB as a learned society) among the 10 studied.
  - The results underline that nanomedicine and organoids are still relatively untapped by the studied organisations, notably business associations.
  - The only occurrence of the term "organoid" comes from the EATCB, with a high frequency (50%) which indicates a significant interest on the part of this learned society in this emerging topic.

### Occurrences of specific terms related to gene and cell within the production of the organisations

	Biological medicine	Orphan medicine	Advanced therapy medicinal product	Gene therapy	Cell therapy	Tissue engineering	Genome editing
European Federation of Pharmaceutical Industries and Associations (EFPIA)	11%	25%	4%	14%	11%	0%	0%
European Associations for Bioindustries (Europabio)	0%	9%	45%	45%	32%	5%	50%
European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)	0%	0%	100%	0%	0%	0%	0%
MedTech Europe	0%	0%	50%	50%	50%	50%	50%
European association of tissue and cell banks (EATCB)	100%	25%	100%	75%	100%	100%	25%
European Society for Blood and Marrow Transplantation (EBMT)	6%	0%	14%	23%	99%	9%	9%
European Eye Bank Association (EEBA)	50%	0%	50%	0%	100%	100%	0%
European Society of Gene and Cell Therapy (ESGCT)	9%	0%	9%	82%	45%	9%	27%
European Industrial Pharmacists Group (EIPG)	0%	0%	100%	0%	0%	0%	0%
European association of hospital pharmacist (EAHP)	17%	33%	50%	0%	0%	0%	0%

### MAIN RESULTS

- ♦ **Advanced Therapy Medicinal Product:** This specific term is the most frequently found in our analysis regardless of the type of organisation studied. It has been found on every organisations' websites. It should be noted that the term does not appear frequently on the ESGCT website although we have not searched for the acronym (ATMP), which may be more frequently used.
- ♦ **Cell Therapy** is the second most frequently used term among the keywords we researched. There is a strong representation of learned societies. All of them have used it frequently.
- ♦ **Tissue engineering, Gene therapy and biological medicine** have been found in the same number of websites (6/10) among the studied organisations. They have been particularly used by learned societies.
- ♦ **Genome editing** has been used by half of the organisations we studied. This specific term is over-represented by the 2 business associations that have mentioned it.
- ♦ **Orphan Medicine** is the most underused specific term among the selected keywords. It has been mentioned by 4/10 organisations only and quite rarely regardless of the type of organisation studied.

## CONCLUSION

- Half of the organisations we studied have one (or more) specific working Group/Committee/Council (hereafter groups) targeting biomedical innovations regarding our keywords and related terms. When these groups exist, they are more frequently found in learned societies (4/5). Among these groups, all have titles closer to our specific keywords than to our general ones.
- Using groups targeting biomedical innovations enabled us to minimise any bias and limits we might have introduced through our choice of keywords: for EUCOPE, no occurrence of "orphan medicine" have been found in our study, but there is a group which targets this type of medicines. Its involvement in this therapeutic area is therefore confirmed.
- The appearance of the term "genome editing" mainly for business associations suggests that this is a subject of interest for the industrial field.
- Although we have considered the EIPG to be a professional organisation representing industrial pharmacists, our study shows many points of convergence with MedTech Europe. This can be explained by the industrial aspect of this organisation.
- Among the learned societies, the 2 associations of banks (EATCB & EEBA) have been the most active. EATCB appears clearly as the organisation using the most our selected keywords among all the organisations studied. EBMT & ESGCT have used quite similarly our keywords with only one significant difference: the emphasis is on gene therapy for ESGCT while it is on cell therapy for EBMT. In our study, the term "gene therapy" occurred 1.8 times more frequently than "cell therapy" for the ESGCT.
- EBMT, ESGCT and EAHP distinguish themselves from the other organisations studied by their number of groups.
- The EBMT and the ESGCT appear to be the two learned societies with the closest links in their areas of interest.

Despite changing its name to include cell therapy, the ESGCT remains more active in the field of gene therapy, which is confirmed by the titles of its working groups.

## Innovative therapy in European Parliament's positions: a numerical science-based vocabulary analysis

**T. ALLOUCHE, V. BRUNEL, F. BECHET, M. GLINEL, A. MAHALATCHIMY**, Innovative therapy in European Parliament's positions: a numerical science-based vocabulary analysis, European Society for Gene & Cell Therapy Congress 2023, Brussels, Belgium, 24-27 October 2023 (POSTER available at <https://shs.hal.science/halshs-04290599v1>)

### Abstract

The European Parliament has regularly been involved in the framing of innovative therapy, including gene and cell therapy.

Through the evolution of European Union (EU) law, the European Parliament has been more and more involved in the adoption of EU binding law. Indeed, the co-decision procedure (i.e. the joint adoption of legislative acts both by the European Parliament and the Council of the European Union) has become the ordinary legislative procedure from the adoption of the Lisbon Treaty in 2007. But the Parliament has also been involved in other types of procedures such as the consultation or cooperation procedures. Such participation takes the form of documents that are called European Parliament' positions. The latter constitute an interesting corpus to be studied where ones want to know more about the fields of activities of the European Parliament as the European institution representing EU citizens.

Focusing on innovative therapy in a wide meaning, this poster aims at conducting an exhaustive study of the mention of terms related to this topic in European Parliament's positions.

From the official website of EU law (EUR-Lex), we constructed a database comprising all positions of the European Parliament, with available metadata. The database was then searched in order to find every occurrence of a selected vocabulary on innovative therapy, including general terms such as "biomedical innovation" or more specific terms such as "gene therapy", "cell therapy" or "advanced therapy medicinal products". We thus were able to see what terms were used and when they were first mentioned, and in what kind of texts they were most present. In our corpus of texts including our selected terms, another point of interest was the way this vocabulary was interconnected, allowing us to group words according to their co-occurrence in documents. From a legislative mapping perspective, we were also able to see which legal basis were more often used, as well as which documents were citing each other. This work is presented under the form of a network graph comprising all documents and their interrelations.

We finally developed thanks to Natural Language Processing methods a model of all documents containing our selected terms in order to find by means of textual similarity metrics other relevant documents for which these terms could have eluded. This complementary corpus could later be used for further research on innovative therapy in European Parliament's positions, beyond our initially selected vocabulary.



I-BIOLEX



UMR 7318  
Droit International,  
Composé et Européen



CERIC

# Innovative therapy in European Parliament's positions: a numerical science-based vocabulary analysis

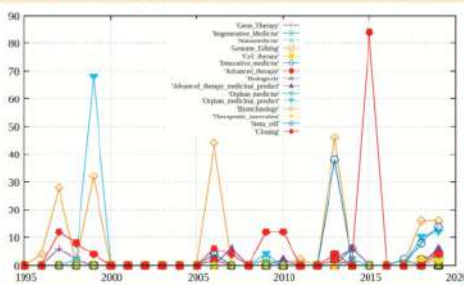
T. Allouche (1), V. Brunel (2), F. Béchet (3), M. Glinel (4), A. Mahalatchimy (5)

1 Masters student in Computer Science, Aix Marseille University  
 2 Research Engineer, CNRS, UMR 7318 International, Comparative and European laws (DICE) CERIC, CNRS, Aix Marseille Univ., Toulon Univ., Pau & Pays de l'Adour Univ., Aix-en-Provence, France  
 3 Computer Science Professor, Director of LIS, UMR 7026 - CNRS / AMU / UTLN  
 4 Post-doctorate fellow in the I-Biolex project, UMR 7318 DICE CERIC, CNRS, Aix Marseille Univ., Toulon Univ., Pau & Pays de l'Adour Univ., Aix-en-Provence, France.  
 5 EuroGCT Deputy coordinator and WP4 leader Permanent, Researcher in law at the French National Centre for Scientific Research (CNRS, chargée de recherche), Law Faculty, UMR 7318 DICE CERIC, CNRS, Aix Marseille Univ., Toulon Univ., Pau & Pays de l'Adour Univ., Aix-en-Provence, France. Contact: valentin.BRUNEL@univ-smu.fr / This work has been supported by ANR-funded I-BioLex project (ANR-20-CE24-0007-01), by the European Union's Horizon 2020 EuroGCT project (GA: No 965241) and the Institut Laue-Langevin (Aix Marseille Université)

**INTRODUCTION.** Through the evolution of European Union (EU) law, the European Parliament has been more and more involved in the adoption of EU binding law. Indeed, the co-decision procedure (i.e. the joint adoption of legislative acts both by the European Parliament and the Council of the European Union) has become the ordinary legislative procedure from the adoption of the Lisbon Treaty in 2007. But the Parliament has also been involved in other types of procedures such as the consultation or cooperation procedures. Such participation takes the form of documents that are called European Parliament's positions. The latter constitute an interesting corpus to know more about the fields of activities of the European Parliament, as the European institution representing EU citizens. Focusing on innovative therapy in a wide meaning, this poster aims at conducting an exhaustive study of the mention of terms related to this topic in European Parliament's positions.

**METHODOLOGY AND CORPUS.** From the official website of EU law (EUR-Lex), we constructed a database comprising all positions of the European Parliament, with available metadata. This metadata mainly includes the date and type of documents, as well as the related legal basis and all instruments cited. The database was then searched in order to find every occurrence of a selected vocabulary on innovative therapy, including general terms such as "biomedical innovation" or more specific terms such as "gene therapy", "cell therapy" or "advanced therapy medicinal products". We thus were able to see what terms were used and when they were first mentioned, and in what kind of texts they were most present. In our corpus of texts including our selected terms, another point of interest was the way this vocabulary was interconnected, allowing us to group words according to their co-occurrence in documents. From a legislative mapping perspective, we were also able to see which legal basis were more often used, as well as which documents were citing each other. This work is presented under the form of a network graph comprising all documents and their interrelations.

## Findings 1.1: Frequency over time and by category of keywords



Using the database from Eur-Lex, our first task was to look for occurrences of our selected vocabulary. The first graph shows through time the frequency of each occurrence.

Graph 1: Frequency of keyword occurrences in our corpus by date

## Findings 2: Networks between documents



In accordance with our objectives, we looked at all instruments cited in every document of our corpus containing at least one of our keywords.

The graph on the left is the result of a network analysis conducted on these instruments. Its principle is straightforward: when a document comprised another as an instrument cited in the Eur-Lex metadata, a link was declared between both. The documents having more relations are thus those either that cited the most documents, or were cited by most, or both.

Graph 2: Network of instruments cited

### Main results

- Among the 7 resolutions the most cited, 3 lead to a directive and 4 to a regulation.
- Only one of the most cited texts relates to a final text that has not been adopted yet (S2022AP0317 on promotion of energy from renewable sources).
- The topics covered by descending order are the following: Animal Health (transmissible animal diseases) > European Maritime, Fisheries and Aquaculture Fund > medical devices > promotion of energy from renewable sources > quality of water intended for human consumption > Internal Security Fund > Industrial emissions (integrated pollution prevention and control)
- Regarding the dates of the most cited texts: 3 are from 2019, 2 from 2014, 1 from 2022, and 1 from 2009

### Main conclusions

- The legal nature of the act to which the resolutions relate does not seem to have an impact on its importance regarding its citation quantity.
- The citation quantity is not linked to the outcome of the legal procedure.
- The topics appear various.
- Nevertheless, they are mainly crossing health and environmental fields.
- Among the 7 different topics, 2 relate to a fund (Fisheries and Internal security)
- Only one text directly relates to pharmaceutical and it covers medical devices and not medicinal products
- The dates of texts range from 2009 to 2022, and mainly from 2014 to 2019.

The analysis of the most cited legal basis has no interest for our studies as it highlights the legal rules for the involvement of the European Parliament in the adoption of legal acts. Indeed, the most cited legal basis are the ones that empowered and framed the involvement of the European Parliament in the legal procedures: mainly Articles of the Treaty relating to the ordinary legislative procedure (current and previous versions), European Parliament's rules of procedures, and adaptation of legal acts for the use of the regulatory procedure with scrutiny. Thus, it relates to the legal technique only and not to the topic of our study.

### Findings 3: Exploratory analysis

Once all documents containing our selected vocabulary were identified, we wished to conduct an automated research of associated documents. The method consists in producing a vector representation of each document in the collection in order to be able to compute a similarity metric. To produce these vector representations, we can define a common vocabulary for all documents and compute a weight for each term in a given document to obtain its vector. Regardless of the method used to produce these vectors, finding new relevant documents consists in looking for the nearest neighbours of target documents in the document vector space. We performed a preliminary experiment following this methodology using the TF/IDF weighting method. Unfortunately, this analysis did not yield interesting results so far, as documents with similar vectors did not seem to match our theme of innovation in biotechnologies. Future research may comprise the use of more advanced weighting methods based on embedding as well as considering document graphs. However, the very strong homogeneity of Parliament resolutions' texts makes this sort of tool difficult to operate.

- All our keywords relating to organoids have never appeared among the EP resolutions: Organoid, Organ on a chip, Body on a chip, Cerebroid, Cerebral organoid, Brain organoid, neural organoid, Gastruloid, Blastoid, Blastoid, Tumouroid.
- 4 keywords have never appeared: Biomedical innovation, Tissue engineering, Advanced medicine, Biological medicine
- 4 keywords have appeared the most: Biotechnology, Cloning, Orphan medicinal product, Stem cell
- Biotechnology has appeared the most and in 20 different documents, by descending order, especially:
  - Around 1998: Research funding (4th framework programme), directive on legal protection of biotechnological inventions, directive on genetically modified organisms (GMOs)
  - Around 2004: Research funding (7th framework programme)
  - Around 2014: Research funding (Horizon 2020) and Regulation related to the Nagoya Protocol on Access to Genetic Resources
  - Around 2020: research funding (InvestEU & Horizon Europe)
  - In 2011: directive on GMOs
- Cloning has also appeared a lot and in 15 different documents, by descending order, especially:
  - In 2015 on a finally withdrawn proposal of a directive on the cloning of animals
  - Around 1998: research funding (fifth framework programme) and directive on the legal protection of biotechnological inventions
  - Between 2007 & 2010: novel foods and on organic production
  - In 2006: research funding (7th framework programme)
  - In 2013: research funding (Horizon 2020)
- Stem cell has also appeared a lot and in 11 different documents, by descending order, especially:
  - In 2013: research funding (Horizon 2020)
  - Around 2020: research funding (Horizon Europe, InvestEU)
  - In 2019: research funding (Horizon Europe, InvestEU)
  - In 2006: research funding (7th framework programme)
- Orphan medicinal product has also appeared a lot and in 7 different documents, by descending order of occurrence, especially:
  - In 1999: Regulation on Orphan medicinal products (most occurrence)
  - In 2019: Regulation on Health Technology Assessment (HTA)
  - In 1998, 2009 on actions on rare diseases and in 2014 on a proposal related to the use of the regulatory procedure with scrutiny
- Advanced therapy medicinal product (ATMP) has not appeared many times, but in 9 different documents, especially:
  - In 2007: Regulation on ATMP
  - In 2010: Regulation on pharmacovigilance
  - In 2014: Regulation on medical devices and proposal related to the use of the regulatory procedure with scrutiny
  - In 2019 & 2020: research funding (Horizon Europe, InvestEU, EU4Health) and a regulation related to the use of the regulatory procedure with scrutiny
- Several keywords that do not appear a lot for a long time have clearly appeared around 2020: therapeutic innovation, genome editing, nanomedicine:
  - Genome editing and nanomedicine in same 2019 text > research funding (7th framework programme)
  - Therapeutic innovation in Regulation on HTA

## Findings 1.2: Clustering of keywords

We then set out to create a series of groups or clusters, based on terms which were more often present in the same documents. Below is the list of every cluster:

### Cluster A: Biotechnology / Stem cell/Cloning

Common texts for these 3 keywords: 7th framework programme, Horizon 2020, InvestEU & Horizon Europe, and directive on legal protection of biotechnological inventions (For Biotechnology and cloning only)  
 => The most common texts relate to research funding.

### Cluster B: Advanced therapy medicinal product/ Advanced therapy/ Gene therapy/ Innovative medicine

There is not 1 common text for these 4 keywords. But: 1 for Advanced therapy, Innovative medicine: Horizon 2020 (2013) and 1 for Advanced therapy, Gene therapy, Advanced therapy medicinal product: Horizon Europe (2019)  
 => They all relate to research funding.

### Cluster C: Nanomedicine/ Genome editing/ Regenerative Medicine/ Cell therapy

Not 1 common text for these 4 keywords. But: 1 for Nanomedicine, RM, Cell Therapy: Horizon 2020 (2013) and 1 for Nanomedicine, Genomedicine: Horizon Europe (2019)  
 => They all relate to research funding.

### Cluster D: Orphan medicinal product/ Orphan medicine/ Therapeutic innovation

2 texts related to Regulation on Health Technology Assessment (2019 & 2018) are common to these 3 keywords, and 1 text related to Action on rare diseases (2009) is common to Orphan medicinal product, Orphan medicine  
 => The most common texts relate to Regulation on Health Technology Assessment.

### On the occurrences of keywords

- As Biomedical innovation, Tissue engineering, Advanced Medicine and Biological Medicine have not been found and are not legal terms, it may be thought that the EP is using preferentially the legal term. Nevertheless, although Orphan medicinal product has been more used than orphan medicine, the latter has been found, even if it is not the legal term.
- Biotechnology has appeared the most both in general texts on research funding and in more specific texts (legal protection of biotechnological inventions, Nagoya Protocol on Access to Genetic Resources, GMOs).
- Cloning has appeared a lot both in general texts on research funding and in more specific texts (proposal of a directive on the cloning of animals, legal protection of biotechnological inventions, novel foods and on organic production).
- Stem cell has also appeared a lot but only in general texts on research funding.
- Orphan medicinal product has also appeared a lot mainly in texts related directly to these products or to rare diseases, but also to Health Technology Assessment.
- ATMP has not appeared many times but in more different documents than Orphan medicinal product (9 vs.7). They relate to ATMP specifically but also to a specific stage of their development phase (pharmacovigilance) and to medical device as a potentially closed legal category and relevant regulation (e.g. Combined ATMP). They also relate to more general topics such as research funding and the use of the regulatory procedure with scrutiny.

### On the networks between documents

- The apparition of our keywords in the most cited texts is not linked to the importance of the final legal act (legal nature) or to the outcome of the legal procedure (adoption or not of the final legal act). Thus, the quantity of citation of a text containing our keywords is more linked to its topic than to its techno-legal context.
- The topics of the most cited texts are transversal to health and environmental issues.
- Contrary to our expectations, our keywords had very little to do with pharmaceuticals, as only one text (on medical devices and not on medicines) in this field stood out.
- There may be an unforeseen parameter on the Eur-Lex website that promotes the most recent texts. This may have biased our results.

While the European Parliament has been known to tackle ethical questions, it has not yet identified organoids as a field to be considered.

In contrast, Biotechnology (e.g., directives on legal protection of biotechnological inventions and on GMOs), Orphan medicinal product (e.g., Regulation on HTA) and Cloning (e.g., withdrawn proposal of a directive on the cloning of animals) have been highly found, and the most found among European Parliament's opinions proposing amendments due to ethical, legal, and societal issues at stake.

Both the analysis by occurrence of keywords and the analysis by clusters of keywords found together show that Biomedical Innovation related keywords appear more in texts related to research funding. Nevertheless, cluster 4 is distinct and specific as none of its keywords (Orphan medicinal product, Orphan medicine, Therapeutic innovation) appear in texts related to research funding.

Both Orphan medicinal product and Advanced Therapy Medicinal Product appear in more various texts (beyond general research funding for the latter) but also texts that have more specific topics as linked to these particularly regulated types of medicinal products.

## Conclusion

## Mapping regulators' early interactions procedures to support innovation

**A. DELAGE, L.-S. GILBERT, A. MAHALATCHIMY**, Mapping regulators' early interactions procedures to support innovation, European Society for Gene & Cell Therapy Congress 2023, Brussels, Belgium, 24-27 October 2023 (POSTER available at <https://hal.univ-lyon2.fr/CERIC/halshs-04290584v1>)

### Abstract

In an effort to help stakeholders to overcome the legal and scientific challenges raised during the development of a medicinal product, procedures, such as scientific advice, have been established in the European Union to enable early contact with regulators, especially in the field of gene and cell therapy. These procedures help to support innovation. They are various: some are available for all medicines and others target innovative medicines or Advanced Therapy Medicinal Products (ATMPs); some are legislative or regulatory schemes, others put into place services; some benefit to all types of medicines' developer, others target a specific type of developer. These procedures for early interactions between stakeholders and regulators are available to facilitate communication between institutions and medicine developers all along the medicine's life-cycle, but the main focus is on the pre-marketing authorisation phase. The exchanges occurring between regulators and the seeker of interaction can impact the chances an ATMP has to enter on the market. Thus, the aim is to foster their development by helping developers to navigate the regulatory pathways adequately for ATMPs to meet quality, safety, and efficacy requirements according to robust evidence to obtain marketing authorisation and access to patients. Knowing all the procedures, who can ask for them, which procedure to use, and with which regulator can be a challenge. Moreover, the extent of the possible support is often overlooked. This poster describes and discusses the multiple existing options available to ATMPs' developers to overcome challenges during the pre-marketing authorisation phase through early interactions with regulators, here focusing on the European Medicines Agency and National agencies. Communicating on the early procedures available at national and European levels will help to identify potential gaps and raise developers' awareness of the different procedures available to support the marketing authorisation of ATMPs.

# Mapping regulators' early interactions procedures to support innovation

Auxane Delage<sup>1</sup>, Luc-Sylvain Gilbert<sup>2</sup>, Dr. Hsin-Yu Kuo<sup>3</sup>, Dr. Anna Couturier<sup>4</sup>, Dr. Aurélie Mahalatchimy<sup>5</sup>

<sup>1</sup>EuroGCT Information Officer on Ethical, Legal & Societal issues (ELSI), Research Engineer and PhD student in law, Law Faculty, UMR 7318 International, Comparative and European laws, DICE CERIC, CNRS, Aix-Marseille Univ., Toulon Univ., Aix-en-Provence, France; <sup>2</sup>EuroGCT Information Officer on ELSI, Research Engineer in law, UMR 7318 DICE CERIC, CNRS, Aix-Marseille Univ., Toulon Univ., Aix-en-Provence, France; <sup>3</sup>EuroGCT Information Officer on ATMP Product Development Pathway, Centre for Regenerative Medicine, Institute for Regeneration and Repair, University of Edinburgh, UK; <sup>4</sup>EuroGCT Project Manager, Centre for Regenerative Medicine, Institute for Regeneration and Repair, University of Edinburgh, UK; <sup>5</sup>EuroGCT Deputy coordinator and WP4 leader, Permanent Researcher in law at the French National Centre for Scientific Research (CNRS CR), Law Faculty, UMR 7318 DICE CERIC, CNRS, Aix-Marseille Univ., Toulon Univ., Aix-en-Provence, France. **Acknowledgements:** This work has been supported by European Union's Horizon 2020 EuroGCT project (GA: No. 895241) and by ANR-funded I-Biolex project (ANR-20-CE20-0077-01).

## Introduction & Aim

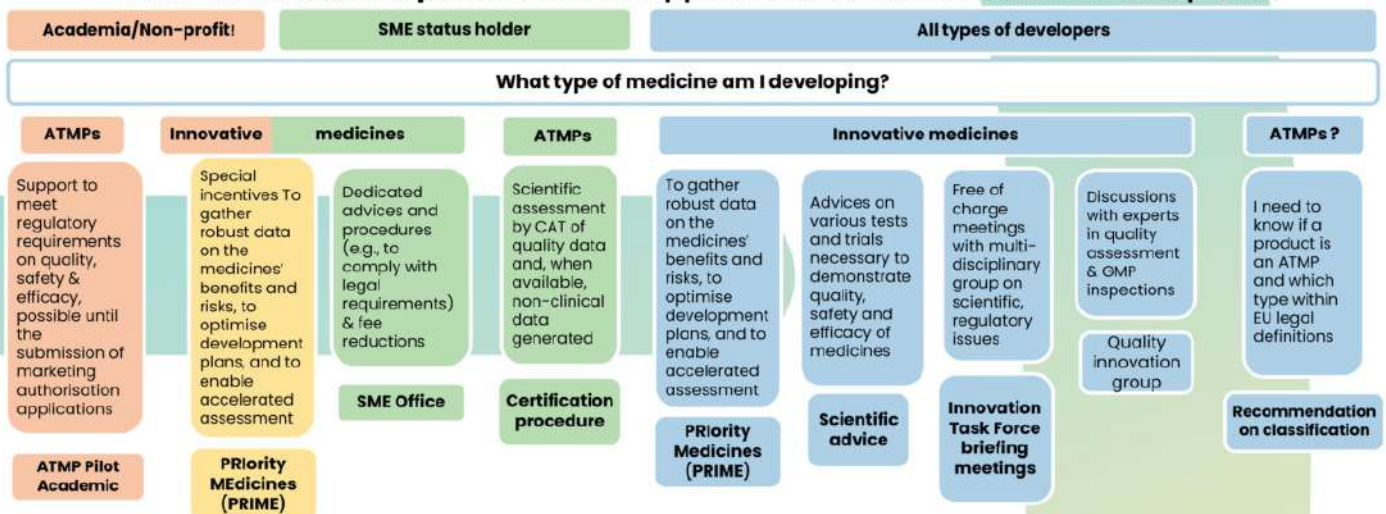
Early interactions procedures with regulators are implemented to support innovative medicines development, and the specific challenges they face.

The support comes in the form of services and regulatory procedures allowing medicines' developers to interact with regulators through existing mechanisms during the development of a medicinal product.

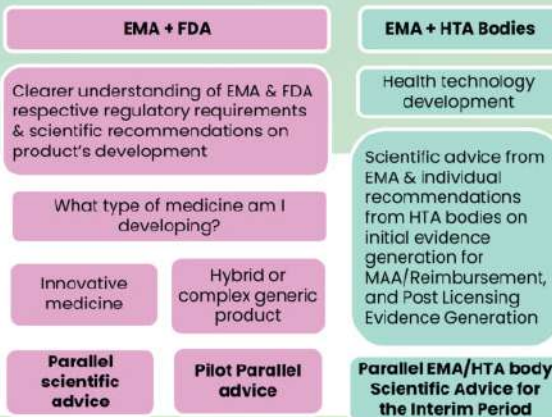
The procedures are generally dependent on the type of product developed, and on the status of the stakeholder trying to contact the regulator early. This entails a case-by-case approach to support innovation. The regulators have designed relevant tools to support different types of actors with specific challenges (SMEs, academia, industry). In addition to dedicated services and procedures, guidance developed by regulators as well as regulators' participation in various meetings also aim to support medicines' development, even though these aspects will not be considered here.

Despite limited human resources (EU and national level), Regulators have established new ways to facilitate dialogue between the institutions and the stakeholders where gaps and needs have been identified. The poster showcases the principal mechanisms in place in the European Union (EU) and in the Member States of the EEA regarding both innovative medicines and Advanced Therapy Medicinal Products (ATMPs) specifically. Communicating on the existing support at both levels bridges the knowledge gap on the existing opportunities for early interactions with regulators.

## EMA's services and procedures to support innovation medicines' development



## Interactions with multiple regulators to support medicines' development

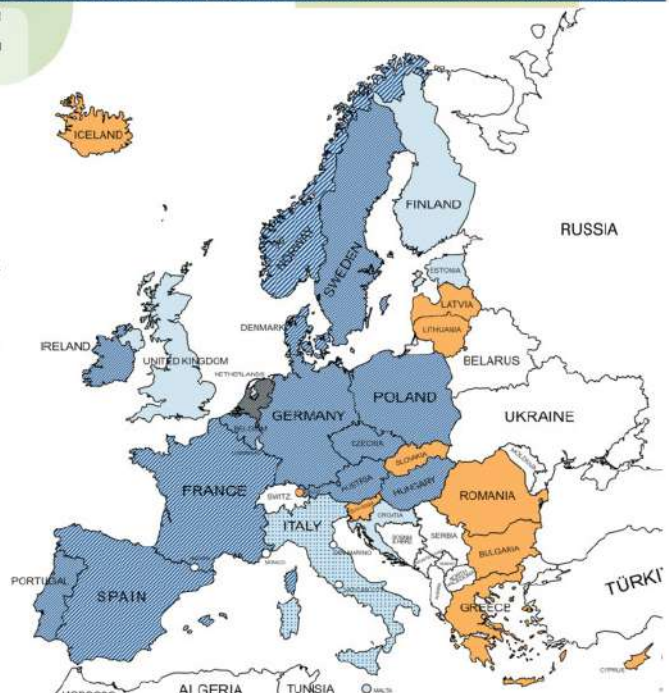


## Interactions with national competent authorities

Medicine developers can contact national competent authorities to interact with one or multiple regulator(s) at national level. List of national competent authorities in the EEA available on EMA's website. **Available Procedures** → scientific advice, Simultaneous National Scientific Advice (ex). **Available Services** → Innovation offices (ex). Some EEA countries have national competent agencies but no innovation offices and do not offer SNSA. No innovation office = No interaction for example Iceland no innovation office but offers scientific advice.

Innovation offices and participation in Simultaneous National Scientific Advice (SNSA) in EEA countries and the UK

- Countries with innovation offices
- Countries without innovation offices
- ▣ Innovation office and leading or participating in SNSA
- ▣ Innovation office and observer role in SNSA
- ⊠ 2 Innovation offices: 1 leading or participating role and 1 observer role in SNSA



FDA: Food and Drug Administration, HTA: Health Technology Assessment bodies, EMA: European Medicines Agency, MAA: Marketing Authorisation Applications, OMP: Orphan Manufacturing Practices

Any contribution is warmly welcome!

Please join the EuroGCT ELSI Network of Expertise: provide draft content of entries, lay summaries of your research papers, to translate existing entries, to review draft entries, to provide useful updated resources.

To get involved in this collaborative work please contact the EuroGCT Information officers on ELSI:

Auxane Delage: [auxane.delage@univ-amu.fr](mailto:auxane.delage@univ-amu.fr)

Luc-Sylvain Gilbert: [luc.gilbert@univ-amu.fr](mailto:luc.gilbert@univ-amu.fr)

All contributions will be credited on the EuroGCT website



## A comparative study of national schemes and services for “early interaction” with Regulators

**A. DELAGE, L.-S. GILBERT, J. VERAN, V. ROBY, A. MAHALATCHIMY,** A comparative study of national schemes and services for “early interaction” with Regulators, ESGCT 2025, 7-10 October 2025, Sevilla, Spain (POSTER available at <https://hal.science/AO-DROIT/halshs-05314257v1>)

### Abstract

Regulators, here understood as national medicines agencies, are supporting the development of innovative medicines in the field of Gene and Cell therapy by creating dedicated schemes and services. These are designed to help developers in the pursuit of making new medicines available for patients. Although such regulatory support can be provided all along the product’s life cycle, regulators generally recommend developers to look for support as early on in the development of a product as possible. Such possibility of obtaining regulatory support can be called “early interaction” with regulators. While “early interactions” existing at the European level are particularly relevant for Advanced Therapy Medicinal Products (ATMPs) for which marketing authorisation is granted under the centralised procedure, the national scale is of the utmost importance. Indeed, the National regulators are most of the time the first contacts for any developer. Beyond the interest in using one’s own mother tongue, several decisions (eg. Clinical trials authorization despite the single application via the European Union (EU) portal), rules and procedures (eg. ATMPs under the hospital exemption) fall under the remit of each Member State. Therefore, the first intention should always be to enter into contact with the regulator of the country where the medicine is developed. However, all countries are not equal when it comes to supporting the development of medicines. The purpose of this research is to identify the opportunities, as well as differences and gaps in availability and choices for developers of innovative medicines seeking early support at the national level. The availability of national support schemes can be a piece of information allowing to complete our understanding of the different national approaches towards gene and cell therapy. Most Member States have procedures for developers to enter into early contact. But a closer look into the available procedures shows discrepancies in the availability and access to regulatory advice across Member States. A possible explanation can be the resources and priorities of the Member State regarding innovative medicines. A few number of countries have no dedicated support procedures or services available to advice medicine developers’ individually. Others have an array of possible schemes for various questions depending on the level of precision and formalism needed by the developers. While most of them have services such as innovation offices or scientific advice, others don’t. Therefore, this study aims to provide a first overview of the available national procedures within the European Economic Area (EEA). Without reaching exhaustivity (due to language barrier and accessibility of resources) but tending towards it, the focus is on establishing a list of different types of available schemes at the national level. By doing so, the study provides starting point comparison and discussion on the choices available across countries and the diversity of the available procedures to support gene and cell therapy development in the EU.



I-BIOLEX



CERIC

# A comparative study of national schemes and services for "early interaction" with Regulators

Auxane Delage<sup>1</sup>, Luc-Sylvain Gilbert<sup>2</sup>, Julie Vêran<sup>3</sup>, Valentin Roby<sup>4</sup>, Aurélie Mahalatchimy<sup>5</sup>

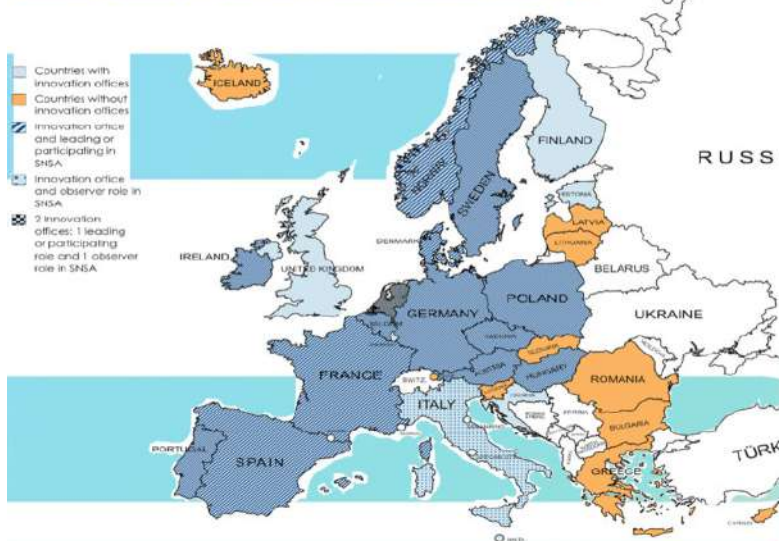
<sup>1</sup>EuroGCT Information Officer on Ethical, Legal & Societal Issues (ELSI), Research Engineer and PhD student in law, Law Faculty, Aix Marseille Univ, CNRS, DCE, Aix-en-Provence, France; <sup>2</sup>EuroGCT Information Officer on ELSI, Research Engineer in law, Law Faculty, Aix Marseille Univ, CNRS, DCE, Aix-en-Provence, France; <sup>3</sup>Cell therapy/Advanced Therapy Medicinal Products' Unit, Center for Clinical Investigation in BiTherapy (INSERM CIC 1409), Marseille University Hospital (AP-HM), Inserm U1029 - AMU - AP-HM - IFC, Marseille, France; <sup>4</sup>Research Engineer in law, EuroGCT and I-Biolex research projects, Law Faculty, Aix Marseille Univ, CNRS, DCE, CERIC, Aix-en-Provence, France; <sup>5</sup>EuroGCT Deputy coordinator and WP4 leader, Permanent Researcher in law at the French National Centre for Scientific Research (CNRS, CR), Law Faculty, Aix Marseille Univ, CNRS, DCE, Aix-en-Provence, France

**Acknowledgements:** This work has been supported by European Union's Horizon 2020 EuroGCT project (GA: No 965241) and by ANR-funded I-Biolex project (ANR-20-CE26-0007-01).

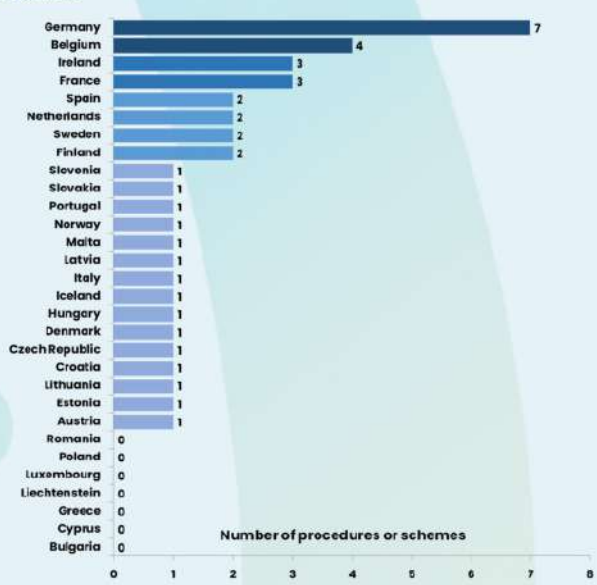
## Introduction & Methodology

National regulators, here understood as National Medicines Agencies, are supporting the development of innovative medicines in the field of Gene and Cell therapy by creating dedicated schemes and services. They are the first contact point for any developer. Beyond the interest in using one's own mother tongue, several decisions (e.g. Clinical trials authorization despite the single application via the European Union (EU) portal), rules and procedures (e.g. ATMPs under the hospital exemption) fall under the remit of each Member State. Therefore, the first intention should always be to enter into contact with the regulator of the country where the medicine is developed. However, all countries are not equal when it comes to supporting the development of medicines. The purpose of this research is to identify the opportunities, as well as differences and gaps in availability and choices for developers of innovative medicines seeking early support at the national level. The availability of national support schemes can be a piece of information allowing to complete our understanding of the different national approaches towards gene and cell therapy. If most Member States have procedures and services for developers' early contact with their availability and access show discrepancies between States. Between September 2023 and September 2025, research and updates have been undertaken on each European Economic Area (EEA) and EU National regulators websites. National regulators have been punctually contacted where information was not found on national websites and when appropriate contact was available. Beyond Simultaneous National Scientific Advice (SNSA) which allows interactions with multiple national regulators, the studied States have also dedicated services (often called innovation offices) and other procedures which this study aims at showing. In the remit of this study the mention N/A is indistinctly used when no services or procedures is available, if nothing has been found or if the information is not provided.

## Innovation offices and participation in SNSA in EEA countries and the UK



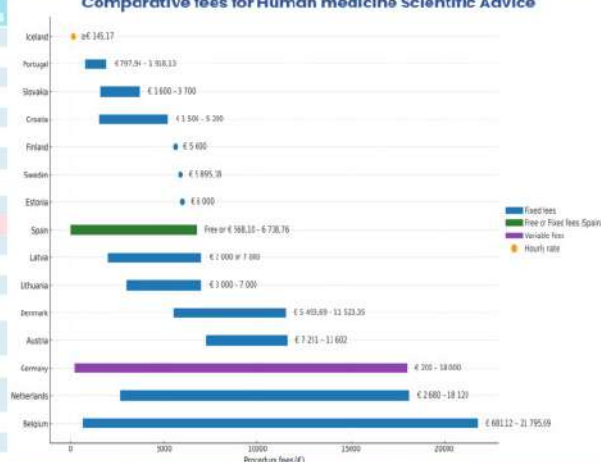
## EEA countries ranked by number of found types of interaction procedures with one regulator



## Scientific Advice procedures and linked fees for human medicines in EEA countries

Country	Status	Name of advice procedure	Fee	Rate basis criteria	Fee incentives
Austria	✓	National Scientific Advice (NASA)	Yes	Novelty of active substance	N/A
Belgium	✓	Scientific-technical advice	Yes	Type of product	Yes
Bulgaria	✗	N/A	N/A	N/A	N/A
Croatia	✓	Scientific advice	Yes	Complexity of request	N/A
Cyprus	✗	N/A	N/A	N/A	N/A
Czech Republic	✓	Scientific advice	Yes	N/A	N/A
Denmark	✓	National Scientific Advice	Yes	Scope of advice	No
Estonia	✓	Scientific advice and pre-submission consultation	Yes	N/A	Yes
Finland	✓	Scientific advice	Yes	N/A	N/A
France	✓	Scientific advice	No	N/A	N/A
Germany	✓	Scientific advice	Yes	Complexity of request	N/A
Greece	✗	N/A	N/A	N/A	N/A
Hungary	✓	Scientific advice / Consultancy	Yes	N/A	N/A
Iceland	✓	Scientific advice	Yes	N/A	N/A
Ireland	✓	General Advice on regulatory requirements and general guidance on technical or scientific issue	Yes	N/A	N/A
Italy	✓	Innovation meeting incl scientific advice	Yes	N/A	N/A
Latvia	✓	Scientific advice	Yes	Type of advice : regulatory or scientific advice	No
Liechtenstein	✗	N/A	N/A	N/A	N/A
Lithuania	✓	Scientific-Regulatory Advice (RSA)	Yes	Stage of development	No
Luxembourg	✗	N/A	N/A	N/A	N/A
Malta	✗	N/A	N/A	N/A	N/A
Netherlands	✓	Scientific advice and Joint scientific advice	Yes	Complexity of request	Yes
Norway	✓	Scientific & Regulatory Advice	Yes	N/A	N/A
Poland	✗	N/A	N/A	N/A	N/A
Portugal	✓	Regulatory & Scientific Advice (RSA)	Yes	Regulatory or scientific + fields (Clinical, pre-clinical...)	N/A
Romania	✗	N/A	N/A	N/A	N/A
Slovakia	✓	Scientific advice	Yes	Complexity and field	No
Slovenia	✓	Scientific advice	N/A	N/A	N/A
Spain	✓	Scientific Advice	Yes	Complexity and field	Yes
Sweden	✓	Scientific advice	Yes	N/A	Yes

## Comparative fees for Human medicine Scientific Advice



## Proportion of EEA countries with found Scientific Advice procedures



Any contribution is warmly welcome! Please join the EuroGCT ELSI network of expertise: provide draft content of entries, key summaries of your research papers, to translate existing entries, to review draft entries, to provide useful updated resources. To get involved in this collaborative work please contact the EuroGCT information officers on ELSI:

Auxane Delage: [auxane.delage@univ-amu.fr](mailto:auxane.delage@univ-amu.fr)  
 Luc-Sylvain Gilbert: [luc.gilbert@univ-amu.fr](mailto:luc.gilbert@univ-amu.fr)  
 Valentin Roby: [valentin.rob@univ-amu.fr](mailto:valentin.rob@univ-amu.fr)

All contributions are credited on the EuroGCT websites.

## Discussion and Conclusion

- Information accessibility**
  - Minor difficulties in finding information
    - Website in at least 2 languages except for Poland
    - Some information are less easy to find like the fees and their related incentives
    - Similar procedures may have different names in different countries
  - Most countries provide accessible information on the available procedures with more or less details.
- Availability of services and procedures**
  - As of April 2025, 1/3 of countries have no innovation office and 2/3 of countries (UK have an innovation office)
  - 23% have no interaction procedure, 50% have one, 26,7% have 2 or more.

- Types of procedures are various: Scientific Advice, Pre-submission meetings, Pathology/innovation meetings, Informal regulatory guidance, Classification services, specific type of advice (e.g. and data protection with EUGA/DIRA in Germany)
- 2 countries have an innovation office for SNSA and no specific national procedure (Poland & Luxembourg)
- 5 countries have specific national procedures but no innovation office (Iceland, Latvia, Lithuania, Slovenia & Slovakia).
- Combining results:**
  - Most countries have available services or procedures (83.3%)
  - Only 3 countries have no services or procedures (Bulgaria, Cyprus, Liechtenstein, Greece, Romania). These are Eastern European countries where dedicated services or procedure may not be needed to answer the demand of developers for early interaction or are not political priorities for the country. An explanation can be the resources and the national priorities of the country.
- In the EEA, national early interactions are generally available and accessible; they are various.

- The procedure of Scientific Advice**
  - Scientific advice (SA) is by far the most available procedure in EEA countries: more than 72% of EEA countries have a procedure of SA, or that can be assimilated to SA (not necessarily the exact same scope)
  - SA fees vary between countries
    - 3 countries have very large scales of prices (Germany, Netherlands & Belgium).
    - The larger the scale the more limiting it could be for developers to know what the final cost will be (e.g. Germany).
    - A higher cost or lack of fee incentives can be linked to some extent to the GMP, available resources and support policies of the country.
    - In countries where fee incentives are available, these are linked to the status of the developer: SMEs, Academia and/or Non-profit org. are targeted similarly to BMA's SA.
  - Scientific Advice is the main interaction procedure with or without payable fees and targeted developers' incentives



# **VII**

## **Guidance**

## Mapping the ATMPs Guidance Landscape

**V. ROBY, A. SCHEER, J. VERAN, F. SABATIER, A. MAHALATCHIMY**, Mapping the ATMPs Guidance Landscape, European Society for Gene & Cell Therapy Congress 2023, Brussels, Belgium, 24-27 October 2023 (POSTER available at <https://shs.hal.science/halshs-04290574v1>)

### Abstract

Relatively new as an autonomous legal category within the European Union (EU) context with the adoption of the Regulation N° 1394/2007 of 13 November 2007 on advanced therapy medicinal products, gene therapy, cell therapy, and tissue engineering medicinal products are also subject of a quite significant amount of soft law production. Indeed, the recent and rapid evolution in these areas and the “youth” of their regulation raise many questions regarding these special rules, their interaction with already existing and more general ones, the requirements for the development of such medicines, their marketing authorisation, their classification, etc. To answer those questions and to dispel as many doubts as possible, guidance documents have been issued by several organisations within the EU context, foremost among them the European Medicines Agency, but also the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) as well as the European Council Directorate for the Quality of Medicines & Healthcare (EDQM) through the publication of the European Pharmacopoeia. This soft law that contributed to regulating ATMPs even before the adoption of specific regulation consists in a disparate collection of documents in terms of types (guidelines/notes for guidance, reflection papers, concept papers, points to consider, position statements, questions and answers, etc.), in terms of topics (scientific guidelines, procedural advices, guidance on clinical trials, on production, manufacture, etc.) and in terms of authors as already mentioned. The result is a sea of texts in which it may be laborious to navigate, especially with ATMPs being biological medicinal products and hence a priori within the scope of guidance for general and biological medicinal products unless specific guidance exists. This is why our contribution, in the form of a poster, seeks to map a landscape of all relevant guidance available in this field to improve access to it and to facilitate its understanding for developers, marketing authorisation applicants and/or holders, academia, health professionals, etc. First by listing and classifying all institutional authors of these guidance documents identified through internet searches, giving the occasion to assess and to graphically visualise the distribution of each one’s contribution in the overall production of such texts, as well as to determine their territorial scope. Second by determining the interactions and overlaps between guidance papers applicable to ATMPs and those applicable to other general or specific medicinal products categories such as biological or biotechnological medicinal products with which ATMPs share the most guidance in common, as well as immunological or blood/plasma medicines and by representing them in the form of easy-to-read diagrams.



I-BIOLEX



**Valentin BOBY** Research Engineer in law, Law Faculty, UMR 7318 International, Comparative and European Law (DICE), CERIC, CNRS, Aix-Marseille University, Toulouse University, Paris and Pápa de l'Auton University, Aix-en-Provence, France.  
**Aaafel SCHEER** Intern in pharmacy, Marseille Public Hospital (AP-HM), Biotherapies Clinical Investigation Center, Marseille, France.  
**Julie YERAN** Responsible of Cell therapy/Advanced Therapy Medicinal Products production at Marseille Public Hospital (AP-HM), Biotherapies Clinical Investigation Center, Marseille, France.

**Florence SABATIER** Professor of Hematology and Biotherapy, Pharmaceutical Sciences Faculty, C2iN INSERM INRAE 1243 AIX-Marseille University, Director of the cell therapy research centre at Marseille Public Hospital (AP-HM), Marseille, France.  
**Arelis MAHALAOTIMY** Permanent Researcher in law at the French National Centre for Scientific Research (CNRS, CR), Law Faculty, UMR 7319 DICE, CERIC, CNRS, Aix-Marseille University, Toulouse University, Paris and Pápa de l'Auton University, Aix-en-Provence, France.

**Acknowledgements:** This work has been supported by the European Union's Horizon 2020 EuroGCT project (101015434) and by ANR funded BioLaw project (ANR-20-CE36-0007-01).

Contact: [valentin.boby@univ-amu.fr](mailto:valentin.boby@univ-amu.fr)

## Introduction and Methodology

Quite early on and well in advance of the adoption of the Regulation N° 1394/2007 of 13 November 2007 on Advanced Therapy Medicinal Products (ATMPs), the European Commission (EC), the European Medicines Agency (EMA), the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the European Directorate for the Quality of Medicines & HealthCare (EDQM) developed guidance documents to address the specific requirements for Gene Therapy (GT), Cell Therapy (CT) and Tissue engineering (TE).

Guidance are here defined as all technical and scientific documents (mainly but not only guidelines) aiming to help medicines developers and marketing authorization applicants to comply with regulatory, ethical and methodological requirements and to better prepare marketing authorization applications.

This poster aims to identify and map all the guidance applicable to ATMPs, taking into account their diverse natures, topics and authors, as well as their potential overlapping with other categories of biological medicinal products.

First, we classified the biological medicinal products according to the European Union (EU) legal nomenclature (Fig. 1).

Then, we compiled and listed all the current guidance related to those different topics, basing our research on the dedicated sections on the above-mentioned institutions websites, and by completing the respective search engines using pre-determined keywords.

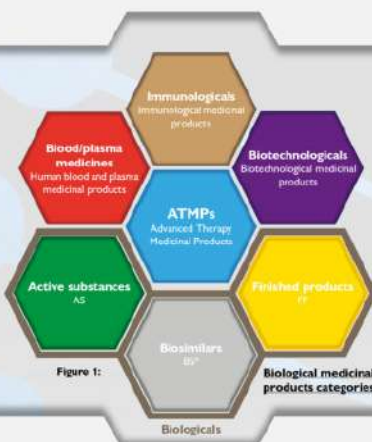


Figure 1:

After deducting the overlapping documents, 213 Current guidances applicable to the 7 different categories of biological medicinal products were listed. To assess the anteriority of these documents, we also sought for their first versions (i.e. first discussed discussions on a specific guidance), reaching the number of 320 available documents: all versions included (First and Current). To these 320 documents we should add to the counting 19 texts from the European Pharmacopoeia (EDQM) texts that we were not able to analyse thoroughly (e.g. no access to their "First" versions, as not being freely accessible).

Focusing on ATMPs, among these 232 Current texts (213 from EMA, ICH and EC and 19 from EDQM):

**105 covered ATMPs (1<sup>st</sup> analysis):** 87 from EMA, ICH and EC and 18 from EDQM, 138 all available versions considered (First, Current and EDQM).

Due to the impossibility to fully access to the 18 EDQM documents applicable to ATMPs, those have been excluded from the more thorough analysis on overlapping, bringing to the number of **120 all-versions-included guidance studied** (from EMA, ICH and European Commission) (2<sup>nd</sup> analysis on overlapping).

\* Biosimilars (BS) that we chose to include in the Biologicals category with Active substances and Finished products with regards to their source and definition.

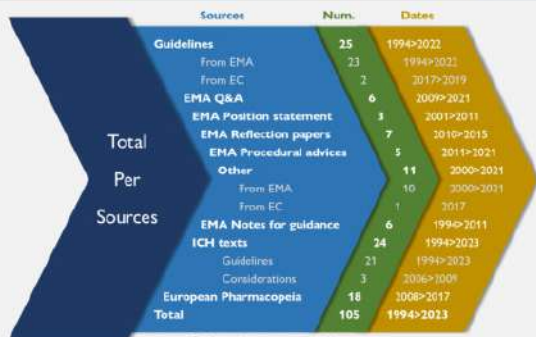


Table 1a: Guidance documents sorted by sources



Table 1b: Guidance documents sorted by categories of ATMPs

- The default type of document for ATMPs keeps being Guidelines or Notes for Guidance (NIG) with 52 on 105 (49,5%).
- Still, heterogeneity of the types of guidance:
  - Many new types of documents emerged from the 2000's: position statements, questions and answers, procedural advices, etc.
  - Category "Other" = quite diverse (points to consider: flowchart, action plan, etc.).
  - Mainly noticeable for "all ATMPs" category.
  - High needs for guidance of all kinds for this dynamic and innovative sector.
- Relatively balanced distribution of guidelines between EMA and ICH among documents applicable to all ATMPs, CT and CT&TE:
  - 23 guidelines authored by EMA (21,9% of the total).
  - 21 guidelines authored by ICH (20% of the total).
  - However, when adding the 6 EMA NIG it brings the EMA Guidelines/NIG number to 29 (27,6% of the total), slightly tempering the latter observation.
- Various distribution of texts according to their authors:
  - EMA = author of the majority of documents (60/105, 57,1%) → Agency function of authorization, supervision and control of ATMPs.
  - ICH = second main author (24/105, 22,9% of the total).
  - EDQM = third main author (18/105, 17,1% of the total).
  - EC = author of fewer documents (3/105, 2,9% of the total).
  - Centrality of the EMA role in the production of soft law for ATMPs at EU level.
- Significantly larger amount of guidance applicable to all ATMPs (62/105, 59% of the total)
  - Among them, only 26 strictly specific to ATMPs. A number remaining higher than for those dedicated solely to GT (24) or to CT&TE (19).

## Analysis based on the list of Current ATMPs guidance

- The 36 left consist in more general-scope documents, most of them being guidelines (28) and NIG (4), mainly issued by ICH (19).
- Most of the time, TE products are covered by documents applicable to both CT and TE
  - Only 1 guidance document from EMA (a Reflection paper) is strictly and solely applicable to TE.
  - CT & TE gathered under a single section on EMA Website (as in our study).
- Relatively close distribution between GT (24 texts, 22,9% of the total) and CT&TE (19 texts, 18,1% of the total). But higher presence of EDQM texts for CT&TE (12) than for GT (6).
- EDQM texts constitute more than half of the guidance applicable to CT&TE (12/19), the rest being composed of "only" 7 EMA documents compared to 13 EMA, 6 EDQM and 5 ICH texts for GT.
- The adoption period running from 1994 to 2023 shows a significantly dynamic sector requiring frequent and up-to-date guidance. However, for CT&TE guidance, the adoption time range is quite shorter (2000 to 2016), while for GT it started earlier (1994) and finished later (2021).
  - Possible explanations:
    - A smaller number of accessible documents specific to CT&TE (12 being non-fully accessible EDQM documents).
    - EMA-legal requirements for CT&TE covered by more general guidance applicable to all ATMPs, or even by broader-scope documents;
    - Strong interest for GT from the beginning of the 1990s as well as recently with the development of CAR-T cells-based medicines.

## Analysis of the individualised overlapping between ATMPs Guidance

This first diagram (Fig. 2) illustrates the overlapping of ATMPs guidance (First and Current versions included) with the individualised other categories of medicinal products. The existing overlapping between those latter is therefore not visible.

- 70/120 (58,3% of the total) strictly specific to ATMPs → Particular needs & requirements for ATMPs.
- Observable strong relation of Biologicals (AS, FP and BS) with ATMPs → Not surprising as ATMPs are biological medicinal products, but:
  - Stronger link with Active substances (31 common guidance, 27,5% of the total) → Transversality of this category.
  - More tenuous link with Finished products (18/120, 15% of the total) → Total number of guidance lower in this category: Finished products are the sub-categories of and for ATMPs (i.e. GT and CT&TE) → Guidance relating to

- Finished ATMPs to be found in documents dedicated to these sub-categories, and not in broader-scope documents.
- Very little intersections with Biosimilars: 2 guidance (1,7% of the total) being the First and Current versions of the same document
  - Absence for now, to our knowledge, of authorised biosimilar ATMP.
- Biotechnologicals = the third biggest intersection (16/120, 13,3% of the total)
  - Relative proximity in terms of requirements;
  - ATMPs equated with Biotechnologicals before adoption of 2007 Regulation on ATMPs.
- Smallest intersections are with Immunologicals with only 2 documents (First and Current version of the same document) shared with ATMPs (1,7% of the total) and with Blood/plasma medicines with only 1 document common with these latter (0,8% of the total).

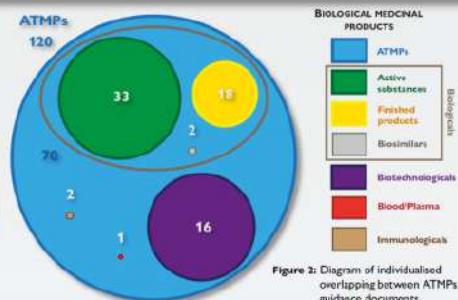


Figure 2: Diagram of individualised overlapping between ATMPs guidance documents

## Analysis of the overall intersections between ATMPs Guidance



Figure 3: Overlapping and non-overlapping between guidance applicable to ATMPs and to other categories of biological medicinal products

- 71/120 (59,2%) do not fall within any of the Biologicals categories (i.e. AS, FP or BS):
  - In addition to the 70 strictly limited to ATMPs, 1 is shared only between ATMPs and Biotechnologicals (0,8% of the total).
  - Confirmation of ATMPs singularity among biological medicinal products.
- Biotechnologicals = the most transversal category in terms of quantity with 15 guidance (12,5% of the total) shared with at least one category other than ATMPs.
  - Blurred differentiation between biological medicinal products and Biotechnologicals in many guidance documents. Transversality confirmed by the fact that Biotechnologicals guidance share at least 2 documents with each one of the other categories except for Blood/plasma medicines.
- Active substances = the second most cross-sectional category in terms of quantity with 14 guidance (11,7% of the total) which also corroborates its transversality. However, Active substances can also be considered as the most encompassing regarding the categories with which it overlaps, sharing at least 1 document with each one of the other categories, including Immunologicals and Blood/plasma medicines.

- Active substances and Biotechnologicals appear closely related
  - The biggest intersection of 7 Guidance (5,8% of the total) between ATMPs, Active substances and Biotechnologicals only.
  - They share 13 guidance documents in total, the maximum of documents shared between two non-ATMPs categories.
  - Confirmation of the importance of Active substances and Biotechnologicals categories within ATMPs guidance.
- Finished products is the most isolated category with 14 documents on 18 shared with nothing but ATMPs.
- The little intersections of ATMPs with Biosimilars and Immunologicals are also shared with Biotechnologicals.
  - Confirms the transversality of Biotechnologicals and the blurred differentiation with the general category of biological medicinal products.
- In contrast, ATMPs/Blood/plasma intersection shared exclusively with Active substances.
  - Blood/plasma category = very isolated not only from ATMPs, but also from other categories of specific biological medicinal products, including the most transversal one (Biotechnologicals).
  - Requirements for Blood/plasma medicines and for ATMPs are very different.



Figure 4: Overlapping between guidance applicable to ATMPs and to other categories of biological medicinal products

## General conclusion

- The singularity of ATMPs is quite well reflected through their guidance landscape with a high number and diversity of specific documents. This shows a strong need of specific requirements inherent to this innovative class of medicines.
- This large quantity and high diversity of guidance may come with complexity and confusion, many documents overlapping.
- Almost no difference is made between CT and TE medicinal products in guidance documents, implying that the legal distinction resulting from the 2007 Regulation on ATMPs is - at least for now - irrelevant for guidance purposes.
- The near absence of link between ATMPs and Biosimilars suggests the latter were not thought for ATMPs. Similar to widely used biological medicinal products, the purpose of their regulation is to make them more accessible and affordable for patients. The fact that very few ATMPs have been authorised and widely used can justify this very little overlapping. Moreover, we could not find any data on the existence of an EU authorised biosimilar of ATMPs (see LS Gilbert & A. Mahalatchimy, Biosimilars of ATMPs - Specificities of the marketing authorization dossier for Biosimilars, EuroGCT website, February 2023, <https://www.eurogct.org/research-pathways/commercialisation/mark-access-atmp/accelerating-marketing-authorisation-3>).



**VIII**

**French policy**

## Organoids and organs-on-chip in gene and cell therapy: which innovation strategies in France?

**A. BOTTACCI, G. NICOLAS, A. MAHALATCHIMY**, Organoids and organs-on-chip in gene and cell therapy: which innovation strategies in France? ESGCT 2025, 7-10 October 2025, Sevilla, Spain (POSTER available at <https://shs.hal.science/halshs-05314478v1>)

### Abstract

Organoids and organs-on-chip (O&OOCs) technologies are quickly becoming ubiquitous in health research and may also offer new perspectives in healthcare in the future. In the field of gene and cell therapy, they are mainly used in pre-clinical development for disease modelling, drug screening and toxicology. They also share a special connection with Advanced Therapy Medicinal Products – the legal category under which they would fall under if used as medicines in the future. To harness their potential, combined efforts from researchers, start-ups, industrial manufacturers, investors and regulatory bodies are required to structure this new technological sector and provide adequate funding. In France, stakeholders involved in pre-clinical and clinical research are organizing themselves around this novel technological sector by establishing new partnerships. Their aim is to standardize practices at the national level to elaborate and define new norms and standards in collaboration with national regulatory agencies that could subsequently be submitted to European decision-makers. In parallel, the necessary funds are being provided under the national strategy *France 2030*, a multiannual, 54-billion-euros plan designed to massively invest in innovative technologies. One of the *Priority research programmes and equipment* (PEPR) under this plan is specifically dedicated to funding research on O&OOCs for 48,4 million euros. *France 2030* also contains an 800 million euros *Health Innovation Plan* with earmarked funds for *Biotherapies and Bioproduction of novel therapies*. Thus, a variety of financing options are available to researchers, start-ups and industry partners that are either working specifically on O&OOCs or using them in their research, including in the development of health technologies. This poster will provide an overview of the ongoing efforts to structure and finance this fast-growing technological sector in France. It will illustrate and discuss how the highly innovative and cross-cutting nature of O&OOCs enables them to benefit from both targeted and broad innovation strategies, including those related to gene and cell therapy. This work aims to support European stakeholders in identifying French networks and potential partners, as well as inspire similar initiatives abroad.

# Organoids and organs-on-chip in gene and cell therapy: which innovation strategies in France?

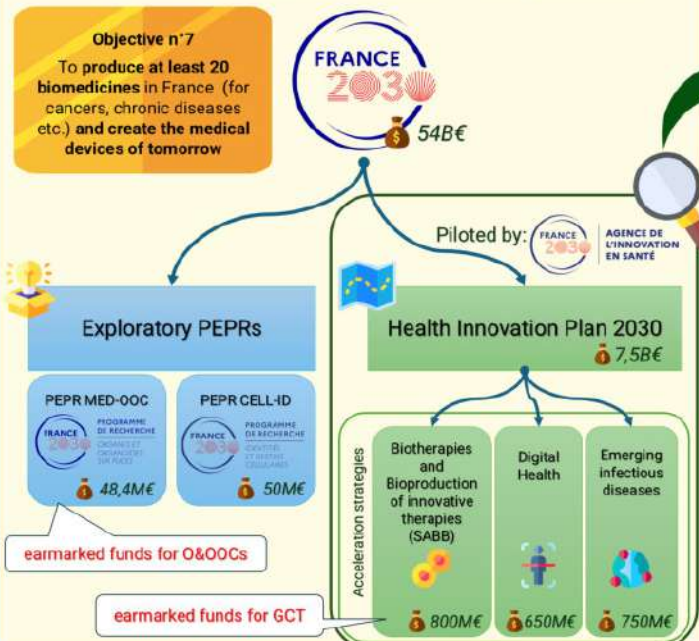
Adrien Bottacci<sup>1</sup>, Guylène Nicolas<sup>2</sup>, Aurélie Mahalatchimy<sup>3</sup>

<sup>1</sup>PhD Student, UMR 7268 ADES, CDSA Health Law Centre - UMR 7318 DICE CERIC International, Comparative and European Laws, Aix-Marseille Université – CNRS, Aix-en-Provence, France ; <sup>2</sup> Professor, UMR 7268 ADES, CDSA Health Law Centre, Aix-en-Provence, France ; <sup>3</sup> CNRS Researcher in law, UMR 7318 DICE, CERIC International, Comparative and European Laws, Aix-Marseille Université – CNRS, Aix-en-Provence, France

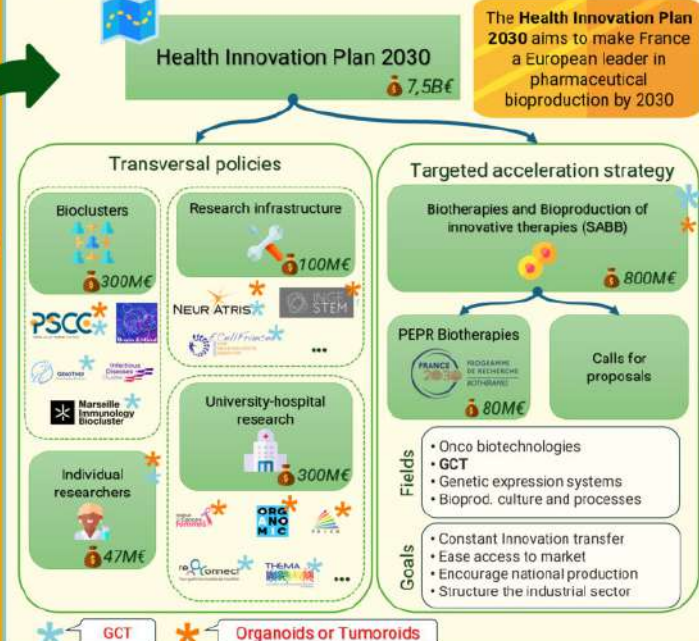
## Introduction

- **Organoids and Organs-On-Chip (O&OCs) technologies** are emerging tools in health research that are quickly becoming ubiquitous.
  - In the field of **Gene and Cell Therapy (GCT)**, they are mainly used in **pre-clinical development** for disease modelling, drug screening and toxicology.
  - If used one day as medicines, they would fall under the legal framework of **Advanced Therapy Medicinal Products (ATMPs)**.
- To harness their potential, combined efforts from researchers, start-ups, industrial manufacturers, investors and regulatory bodies are required to **structure the sector and secure funding**.
  - The main thrust of public funding comes from the national strategy **France 2030**, a multiannual, 54-billion-euros plan designed to massively invest in innovative technologies.
  - Part of it is the **Health Innovation Plan 2030 (Plan Innovation Santé 2030)** designed to **ramp up the national production of biomedicines** in France.
- **How do these French funding policies contribute to the framing of the O&OCs and GCT sectors?**

### France 2030: exploratory and strategic policies



### Health Innovation Plan: preparing the future of healthcare



- **Priority Research Programmes and Equipments (PEPRs): direct support for O&OCs of low technological readiness.**
  - **PEPR MED-OOC** : creating a new generation of biological models on chips to reproduce the functioning of organs.
  - **PEPR CELL-ID** : deploy interception medicine in the field of paediatric brain cancer research.
- **Health Innovation Plan 2030:**
  - Piloted by the Health Innovation Agency (*Agence Innovation Santé*)
  - **Strategic and systemic approach** to health innovation:
    - Address **under-investment and de-industrialization** of the sector.
    - Develop a better health system: **more predictive, more preventive, more innovative** and more personalised.
    - National production of biomedicines to **control costs** of healthcare.
  - Subdivided in three **Acceleration Strategies**, with one providing **direct support for GCT**

- The Health Innovation Plan 2030 actually includes O&OCs within its approach to GCT:
- **Transversal policies: indirect support for GCT and O&OCs**
    - Fund **individual researchers**
    - Create **bioclusters**
    - Develop **research infrastructures**
    - Facilitate **university-hospital research**
  - **SABB Acceleration policy: direct support for GCT and indirect support for O&OCs**
    - From **basic research (PEPR)** to **industrialisation (calls for proposals)**
    - Cell quality & safety standards, Good Laboratory Practices, etc... are relevant for both O&OCs and GCT.

Most of the ongoing and future funding calls are accessible from the website of the French National Agency for Research (<https://anr.fr/>)

## Conclusion

- **O&OCs are cross-cutting technologies**
  - Present **across many innovation strategies**.
  - Their **role is going to grow even more** in the future when they will be technologically mature.
  - O&OCs can be used **throughout the GCT development pipeline**.
  - Most projects financed by the presented strategies already produce O&OCs.
- **Direct and indirect funding for O&OCs**
  - O&OCs benefit from several French innovation funding policies including those related to **GCT**.
  - France has chosen to support O&OCs directly, and indirectly as part of the development of biotherapies.
    - Although organoids are **not explicitly part of the Health Innovation Plan** (they are not medicines as of today), **O&OCs methodologies** can be included in ATMPs projects' applications in the PEPR Biotherapies.
    - The fundings cover research programmes, infrastructures, individuals, equipment and the creation of bioclusters which are relevant for both O&OCs and GCT.
- **Significance of the French strategies**
  - Overall approach recognising both the distinct and linked needs of O&OCs and GCT.
  - Acknowledgement and support of the interest of O&OCs both **in GCT development** and **as future GCT**.