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

Luc-Sylvain Gilbert[1], Auxane Delage[2], Dr. Hsin-Yu Kuo[3], Dr. Anna Couturier[4], Aurélie Mahalatchimy[5]

[1]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; [2]EuroGCT Information Officer on ELSI, Research Engineer and PhD student in law, Law Faculty, UMR 7318 DICE CERIC, CNRS, Aix Marseille Univ, Toulon Univ, Aix-en-Provence, France; [3]EuroGCT Information Officer on ATMP Product Development Pathway, Centre for Regenerative Medicine, Institute for Regeneration and Repair, University of Edinburgh, UK; [4]EuroGCT Project Manager, Centre for Regenerative Medicine, Institute for Regeneration and Repair, University of Edinburgh, UK; [5]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. **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*

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 Pharmacopeia 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)**
  - 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;
  - Questions & answers on comparability considerations for ATMPs, 2019, (EMA/CAT/499821/2019);
  - 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);
  - Guideline on the quality, non-clinical & clinical aspects of gene therapy medicinal products, 2018, (EMA/CAT/80183/2014);
  - Guideline on quality, non-clinical & clinical requirements for investigational advanced therapy medicinal products in clinical trials, 2019, (EMA/CAT/852602/2018)
  - 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

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

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 ATMP's manufacturers

Conduct on-site inspections

Are responsible for the official release of the baches by the control 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.