Current gaps and challenges in CMC aspects of gene therapy medicinal products development in Europe

Oriol Verdú i Bautista [1,2], Ricard Andreu [2], Consol Bozzo [2], Miguel Chillón [1,3]

[1] Universitat Autònoma de Barcelona, Cerdanyola del Vallès, Spain; [2] Asphalion SL, Barcelona, Spain; [3] Viral Vector Production Unit (UPV), Bellaterra, Spain

INTRODUCTION

Gene therapies are continuing to expand their presence in Europe, with multiple approved therapies and numerous ongoing clinical trials. Despite this progress, the so-called Chemistry, Manufacturing and Controls (CMC) requirements for these advanced treatments remain difficult to meet. **This study aimed to identify the key CMC challenges in gene therapy development** through a review of existing evidence. In addition, current strategies proposed to address these challenges were identified, and gaps in existing regulatory guidance were highlighted, with the overall objective of contributing to the continuous improvement of regulatory frameworks and facilitating the progression of gene therapy products from development to commercial application.

METHODOLOGY

- Systematic **review of scientific literature** (2015–2025) was conducted in PubMed, Scopus, and Web of Science using "gene therapy," "CMC," and "challenge" as primary search terms.
- Publicly available European Public Assessment Reports (**EPARs**) and withdrawal assessment reports on **26 EMA gene therapy submissions** were reviewed to identify frequently cited CMC issues.
- **Gaps** in **European regulatory guidance** were assessed by comparing pertinent EMA and FDA guidelines.

CONCLUSIONS

- Main CMC issues in GTMP development in both published literature and evaluated EMA applications: **impurities, potency assays, GMP compliance, characterisation, comparability studies** and **stability.**
- **Harmonised regulatory frameworks and guidance is still evolving**, specially between the U.S. and Europe.
- More **focused guidelines on the primary CMC difficulties** for GTMP development remains a pressing need in Europe.
- **Addressing these challenges at early developmental stages** and **cooperation between developers and regulators** are essential to accelerate patient access.

RESULTS

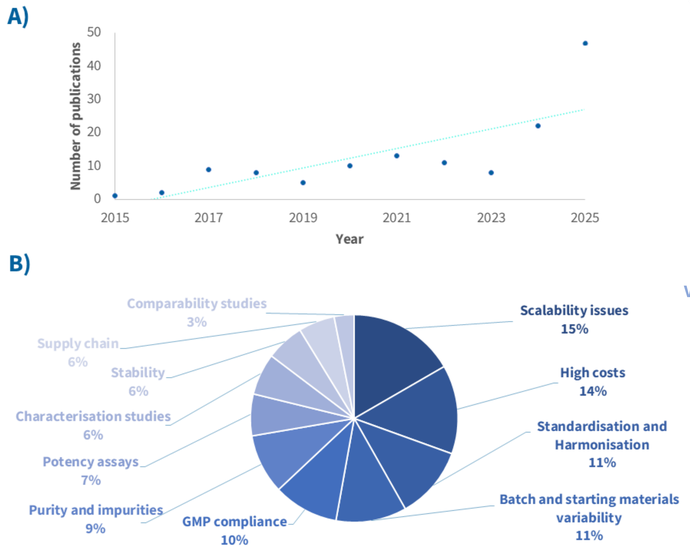

Figure 1. Scientific publications analysis and main CMC challenges detected. (**A**) Line graph of the number of publications addressing CMC challenges of GTMP development from 2015-2025. (**B**) Pie chart of the main challenges in CMC aspects of GTMP development detected in published scientific literature by relative abundance.

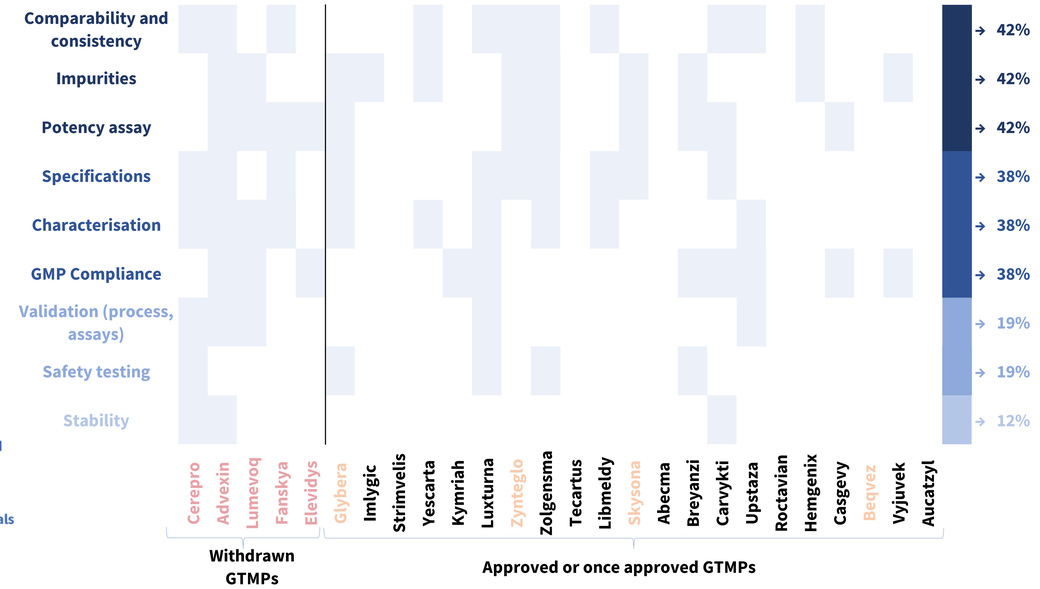

Figure 2. Heat map of the main challenges in CMC aspects of GTMP development detected in approved or withdrawn products. GTMPs withdrawn due to negative benefit-risk assessment are represented in red, while therapies which were withdrawn or had their authorisation expired after authorisation are represented in orange. Currently approved products are shown in black. Percentage represents relative abundance of each CMC challenge in the total 26 GTMPs analysed.

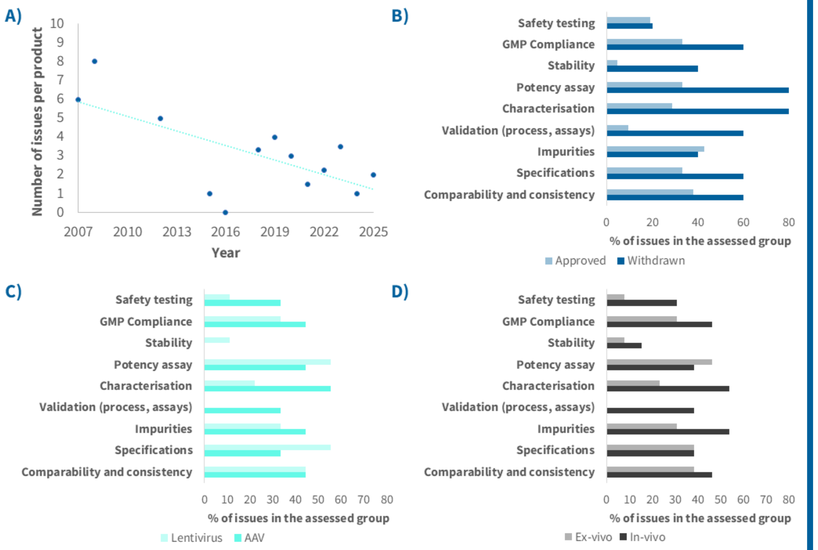

Figure 3. Analysis of the main challenges in CMC aspects of GTMP development detected in approved or withdrawn products. (**A**) Line graph of the number of assessed quality issues per product considering the date of approval or withdrawal. (**B**) Horizontal bar chart of the percentage of issues between approved and withdrawn products. (**C**) Horizontal bar chart of the percentage of issues between ex-vivo and in-vivo therapies. (**D**) Horizontal bar chart of the percentage of issues between therapies using AAV or lentivirus vectors.

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