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# COMPARATIVE QUALITY ASPECTS OF GENE THERAPY MEDICINAL PRODUCTS AND MEDICINAL PRODUCTS CONTAINING GENETICALLY MODIFIED CELLS

Aurélien Mahalatchimy<sup>1</sup>, Eloïse GENNET<sup>2</sup>, Véronique ANDRIEU<sup>3</sup>, Marion FERAUD<sup>4</sup>, Victoire LACAÏLLE<sup>4</sup>, Julie VERAN<sup>5</sup>, Florence SABATIER<sup>6</sup>, Michael MORRISON<sup>7</sup>

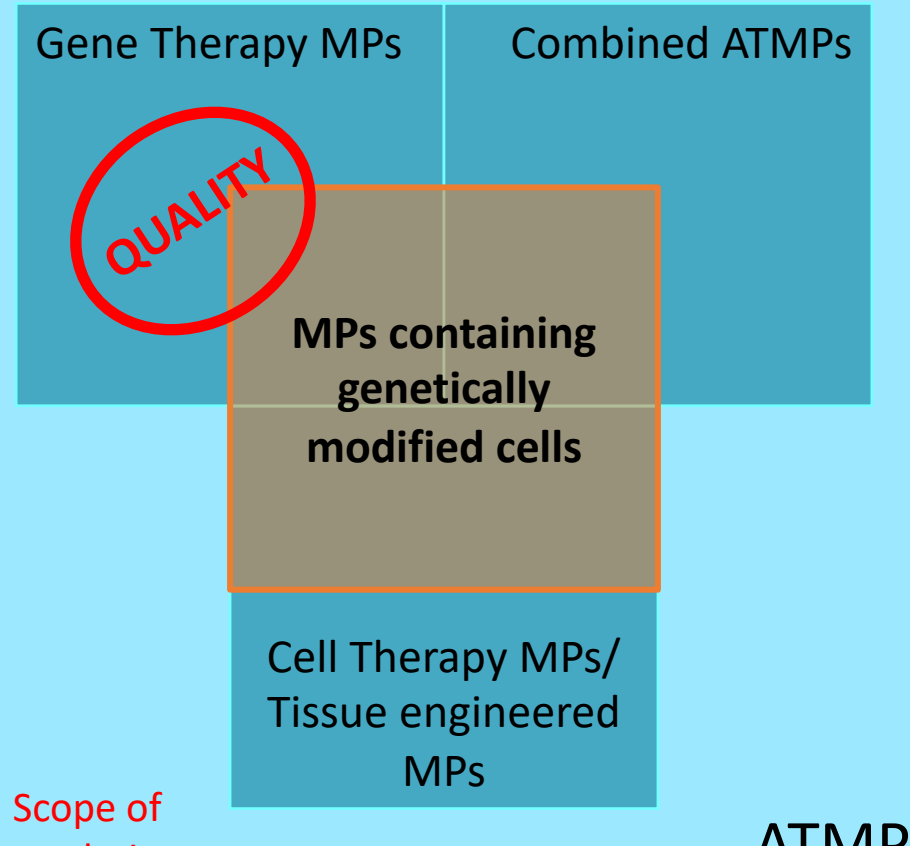
<sup>1</sup>Permanent Researcher in law at the French National Centre for Scientific Research (CNRS, chargée de recherche), Law Faculty, UMR 7318 International, Comparative and European laws (DICE) CERIC, CNRS, Aix Marseille University, Toulon University, Pau & Pays de l'Adour University, Aix-en-Provence, France; <sup>2</sup>Post-doctoral Researcher in Law, Law Faculty, UMR 7318 DICE CERIC, CNRS, Aix-Marseille University, Toulon University, Pau & Pays de l'Adour University, Aix-en-Provence, France; <sup>3</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, Marseille, France; <sup>4</sup>Students in 4th year of Pharmaceutical Sciences, Aix-Marseille University, France; <sup>5</sup>Responsible of Cell therapy/Advanced Therapy Medicinal Products' production at Marseille Public Hospital (AP-HM), Biotherapies Clinical Investigation Center, Marseille, 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), Marseille, France; <sup>7</sup>Senior Research Fellow in Social Sciences, Centre for Health Law and Emerging Technologies (HeLEX), University of Oxford, Oxford, United Kingdom. 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

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 sub-category 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.

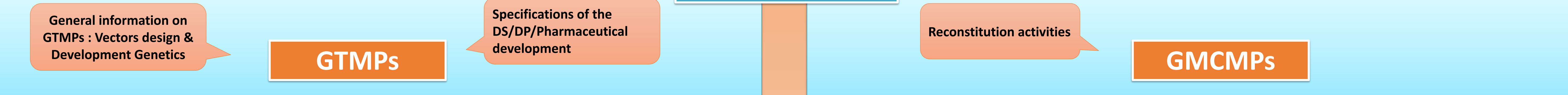


ABBREVIATIONS	Practice
ATMPs : Advanced Therapy Medicinal Products	GTMPs : Gene Therapy Medicinal Products
Combined ATMPs : ATMPs integrating a medical device	ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
CTMPs : Cell Therapy Medicinal Products	MPs : Medicinal Products
DP : Drug Product	TEPs : Tissue Engineered Products
DS : Drug Substance	TSE : Transmissible Spongiform Encephalopathies
EMA : European Medicines Agency	RVC : Replication Competent Virus
GMCMPs : Medicinal Products based on genetically modified cells	
GMP : Good Manufacturing	

## Common topics

Starting material		Other materials, reagents and excipients		Changes in manufacturing process		Manufacturing process	
GTMPs	GMCMPs	GTMPs	GMCMPs	GTMPs	GMCMPs	GTMPs	GMCMPs
<ul style="list-style-type: none"> <li>Same amount of data for each starting material</li> <li>Controlled and optimal storage conditions ensuring maintenance of critical characteristics for intended use</li> <li>Listing + information on source (human, animal), quality and control of these materials</li> </ul>	<ul style="list-style-type: none"> <li>Tools used to genetically modify human/animal cells</li> <li>Types of cells</li> <li>Additional substances combined with manipulated cells</li> </ul>	<ul style="list-style-type: none"> <li>Various materials covered, either as excipients with a wide meaning, or as "other materials and reagents" in addition to excipients</li> <li>References to the European Pharmacopoeia, but to different parts of chapter 5</li> <li>To consider risk of transmitting agents causing TSE</li> </ul>	<ul style="list-style-type: none"> <li>Complexing materials considered as excipients or other materials</li> <li>Various materials to be conducted for complexing materials, (non-viral, viral and non-conventional) adventitious agents</li> <li>Various materials including excipients, materials and reagents used for cell culture, transduction/transfection processes &amp; subsequent steps</li> <li>Specific attention to recombinant proteins and use of structural components, and viral safety</li> </ul>	<ul style="list-style-type: none"> <li>both changes in product/DP and starting materials/DS regarding impact of any process change,</li> <li>appropriate comparability studies to compare pre- and post-change product</li> <li>reference to ICH Q5E,</li> <li>justified choices of criteria/methods use for comparability testing, additional non-clinical/clinical studies</li> </ul>	<ul style="list-style-type: none"> <li>Appropriate comparability studies also to assess the impact of any observed difference on the quality attributes as it relates to products' safety &amp; efficacy</li> <li>Reference to Q&amp;A on comparability considerations for ATMPs</li> <li>Very detailed on comparability studies for changes in manufacturing process of recombinant starting materials, in cell starting material, &amp; in active substance/finished product manufacturing process</li> </ul>	<ul style="list-style-type: none"> <li>Implementation of process parameters and control procedures for design &amp; manufacturing process</li> <li>Clear definition of drug substance &amp; production batch</li> <li>Demonstration of absence of RCV based on sensitive assays.</li> <li>Covering unintended variability resulting in quantitative and/or qualitative differences in product/DS quality or impurities presence</li> <li>Emphasis on number of passages for cell production (GMCMPs) or between the working seed/cell lot and vector production (GTMPs)</li> <li>Implicit (GTMPs) or explicit (GMCMPs) reference to risk-based approach guidelines</li> <li>Various manufacturing risks according to type of product, nature/characteristics of the starting materials &amp; level of complexity of manufacturing process</li> <li>Purification process to be considered</li> <li>Seed/cell bank system to be established &amp; controlled</li> <li>Reference to ICHQ5D</li> </ul>	<ul style="list-style-type: none"> <li>References to guidelines on GTMPs and cell-based MPs</li> <li>Emphasis on Cell preparation and culture</li> <li>Focus on genetic modification of cells as a manufacturing step affected by a variety of inputs</li> <li>Further manufacturing steps (including purification process) other than genetic modification to be considered</li> <li>In-process controls very detailed (to be performed at key intermediate stages) and linked to Critical Quality Attributes</li> <li>Retention samples should be stored for future analysis</li> </ul>
Characterisation		Process validation		Stability studies		Quality Controls	
GTMPs	GMCMPs	GTMPs	GMCMPs	GTMPs	GMCMPs	GTMPs	GMCMPs
<ul style="list-style-type: none"> <li>Rigorous characterization studies through development process</li> <li>Targeting both the medicinal product alone (i.e. DS= genetically modified cells for GMCMPs) or in combination with a medical device</li> <li>Use and description of a range of appropriately qualified molecular, biological and immunological methods</li> <li>To identify and quantify the levels of impurities</li> <li>To address the risk deriving from insertional mutagenesis (GTMPs: for viral vectors)</li> <li>Test to show homogeneity (of the recombinant viral genome or plasmid, for GTMPs) and genetic stability</li> </ul>	<ul style="list-style-type: none"> <li>Definition of degree of purity (percentage of genetically modified cells)</li> <li>Identity testing to detect presence of specific cell population &amp; intended genetic modification before potency tests to determine cells functional properties achieved by the genetic modification, but also cell viability.</li> <li>Data on vector release/replication competence, vector copy number per transduced/transfected cell, transduction/transfection &amp; transgene expression efficiencies</li> <li>Two specific cases targeted: T-cells as an example, cells modified using genome-editing tools</li> </ul>	<ul style="list-style-type: none"> <li>Variable numbers of batches needed</li> <li>Validation for transport</li> </ul>	<ul style="list-style-type: none"> <li>Reference to EMA Guideline on human cell-based MPs</li> <li>List of specific aspects to be considered, e.g., vector copy number</li> <li>Reference to guidelines on GMP for ATMPs</li> <li>Highlights on specific cases: limited availability of cells/tissues, use of manufacturing platform, use of certified automated equipment</li> <li>Validation of storage and transport conditions if occurrence of intermediates' storage</li> </ul>	<ul style="list-style-type: none"> <li>To be conducted for both types of products</li> </ul>	<ul style="list-style-type: none"> <li>Only a few indications on stability studies</li> <li>Reference to the guideline on human cell-based medicinal products only</li> <li>Emphasis on quantitative characterization studies to be both "stability indicative" and "able to detect clinically meaningful changes in the product".</li> </ul>	<ul style="list-style-type: none"> <li>Release testing including performance analysis of quantity, identity, purity, impurities and potency</li> </ul>	<ul style="list-style-type: none"> <li>Copy number of integrated vectors per transduced/transfected cell as read-out for safety and potency to be tested on each batch of final product</li> <li>Emphasis on specific product/process: genome-edited products, cells transduced with replication defective vector</li> <li>Emphasis on specific cases: foreign genetic material removed/eliminated from final product, impossibility to performing release testing on a current product, exceptional two-step release testing program</li> </ul>
GTMPs		GMCMPs		GTMPs		GMCMPs	
<ul style="list-style-type: none"> <li>Demonstration of intended action of regulating, repairing, replacing, adding or deleting a genetic sequence (i.e. biological activity)</li> <li>Emphasis on data confirming: therapeutic gene sequence &amp; genetic elements required for selectivity/regulation/control of the therapeutic sequence;</li> <li>Characterisation of the vector with specificities for viral vectors, plasmids, complexed nucleic acid vector, bacterial vectors, and transformed bacteria.</li> </ul>	<ul style="list-style-type: none"> <li>Compliance with ICH guidelines</li> <li>Setting of reference batch of vector of assigned potency (with stability profile and relevant storage conditions) to standardise assays where appropriate.</li> <li>Discussion, justification &amp; comparison of differences between tests proposed for release of commercial batches and those used for clinical development.</li> </ul>	<ul style="list-style-type: none"> <li>Use of sufficient number of consecutive production runs representative of commercial scale manufacturing process</li> <li>Reference to ICH Q11</li> <li>Potential demonstration of ability of the process to remove or inactivate any helper, hybrid or replication competent viruses generated/used during manufacture or components of the production system</li> <li>Highlights on specific cases: use of scaled down experiments, product subjected to hold times during manufacturing process</li> <li>Validation of shipping and reconstitution</li> </ul>	<ul style="list-style-type: none"> <li>Much more detailed</li> <li>Reference to ICH Q5C on Stability testing of biotechnological/biological products</li> <li>Different types of studies targeted: real time stability studies and forced degradation studies are the main ones, accelerated stability studies may be complementary</li> <li>To cover: DS, DP, any intermediate product stored during production, vector integrity, biological potency and strength, container-closure system used, and proposed shelf-lives and storage conditions</li> <li>Specificities emphasised for shelf-life specifications, products formulated with carrier or support materials, in-use stability of DP, impact of transport conditions for DS/DP with short term shelf life</li> </ul>	<ul style="list-style-type: none"> <li>Compliance with ICH guidelines</li> <li>Setting of reference batch of vector of assigned potency (with stability profile and relevant storage conditions) to standardise assays where appropriate.</li> <li>Discussion, justification &amp; comparison of differences between tests proposed for release of commercial batches and those used for clinical development.</li> </ul>			

## Specific topics



## Discussion and Conclusion

### Questionable cross-references between guidelines

#### More general approaches for GTMPs than for GMCMPs

- Starting Materials: tests to be conducted depend on product & production process (i.e. genetic manipulation for GMCMPs)
- Manufacturing process: While the GTMPs text distinguishes manufacturing process and process controls of DS and DP, the GMCMPs text focus on cell preparation and culture, and genetic modification as main manufacturing step although further steps are also considered.
- Quality controls: Possibility to use reference batch for GTMPs assays standardization seems not possible for GMCMPs targeting distinct product/process/case

#### Changes in the manufacturing process as the topic with most similarities

- The main difference between the two texts is that the GMCMPs text is more detailed than the GTMPs one regarding comparability studies

#### Process validation as the topic with most differences

- One of the most significant differences is that "reconstitution" is not part of the manufacturing process to be validated for GMCMPs by opposition to GTMPs. It is only mentioned 3 times in the GTMPs text while it is a dedicated specific section for GMCMPs.

#### Link between characterization & release criteria

- It appears there is a close link between characterization and release criteria, but it is explicitly mentioned only in GMCMPs text.

#### Specifications highlighted for GTMPs only

- The GTMPs text has sections dedicated to the specifications of DS, DP, and pharmaceutical development. However, specifications appear disseminated within the GMCMPs text. Interestingly, the word "specification" appears only 3 times in the GMCMPs text, and 2 times only in the quality part for "release specification" regarding changes in the manufacturing process of recombinant starting material, and characterization.

1) Some references to other guidelines appear only in the GTMPs text while they are relevant to GMCMPs

- Regarding Other materials, reagents and excipients: Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a medicinal product, Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents, ICH Q5A(R1) on Quality of biotechnological products: viral safety evaluation of biotechnology products derived from cell lines of human or animal origin
- Regarding characterization: section 3.4 of Part IV of Annex I to Directive 2001/83/EC on Specific requirements for ATMPs containing devices
- Regarding Process validation: ICHQ11 Development and manufacture of drug substances (chemical entities and biotechnological/biological entities)
- Regarding Quality Controls: ICH guidelines in general
- Regarding Stability Studies: ICH Q5C Stability testing of biotechnological/biological products

Developers may not be aware of existing relevant useful guidelines

2) While GMCMPs can be both GTMPs or CTMPs, the GMCMPs text refers more to the guidelines on Cell-based MPs than to the GTMPs text

- Reference to the Cell-based MPs text & not to GTMPs text regarding characterization, process validation, and stability studies
- Reference to both Cell-based MPs text & GTMPs text regarding manufacturing process

3) Some references to other guidelines appear only in the GMCMPs text while they are relevant to GTMPs

- Regarding Process validation: Guidelines on GMP for ATMPs
- Regarding Changes in the manufacturing process: Q&A on comparability considerations for ATMPs

It implies the wrong feeling that GMCMPs will be more often qualified as Cell-based MPs: the GMCMPs text has been revised, especially to cover T-Cells but authorised ATMPs based on T-cells (Yescarta, Kymriah, Tecartus) have been classified as GTMPs: more balanced reference to both GTMPs & Cell-based MPs texts would be necessary.

A later date of adoption can explain this absence for the Q&A on comparability considerations for ATMPs