Interactions with regulators for gene and cell therapy-based medicines to reach both the European and US markets

Aurélie Mahalatchimy[1], Auxane Delage[2], Luc-Sylvain Gilbert[3], Valentin Roby[4], Christian Chabannon[5]

[1] 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; [2] Research Engineer and PhD student in law, EuroGCT Information Officer on ELSI, Law Faculty, Aix Marseille Univ, CNRS, DICE, CERIC, Aix-en-Provence, France; [3] EuroGCT Information Officer on ELSI, Research Engineer in law, Law Faculty, Aix Marseille Univ, CNRS, DICE, CERIC, Aix-en-Provence, France; [4] Research Engineer in law, EuroGCT and I-BioLex research projects, Law Faculty, Aix Marseille Univ, CNRS, DICE, CERIC, Aix-en-Provence, France; [5] Centre de Thérapie Cellulaire. Institut Paoli-Calmettes Comprehensive Cancer Center & module Biothérapies du Centre d'Investigations Cliniques de Marseille, Inserm CBT-1409 –AMU –AP-HM -IPC.

Acknowledgments: This work has been funded by the French National Agency for Research (ANR) ANR-funded I-BioLex project (ANR-20-CE26-0007-01) and by the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 965241 (EuroGCT project).

Background & Method

Gene and cell therapy-based medicines are expensive, and are often developed to treat rare diseases on a global scale.

Organisations in place for marketing approval and reimbursement negotiations somewhat differ in Europe and in the United States of America (USA). In the European Union, the European Medicines Agency (EMA) is in charge of assessing marketing authorisation (MA) dossiers filed by Advanced Therapy Medicinal Products (ATMPs) developers, with a view for centralized authorisation in GMP conditions, and commercialization on EU markets. On the basis of the EMA's recommendations, the European Commission then grants or not a marketing approval for defined indication(s), that can be later on extended to additional indications when the MA holder provide additional data. In the USA, the Food & Drug Administration (FDA) is in charge of both assessing and granting marketing authorisations for "Advanced Therapies" (corresponding to ATMP in the EU).

There is a global perception that market access is restrained by long delays and insufficient reimbursement of these complex medicines. In order to mitigate these difficulties, measures have been taken that promote early-contacts between developers / pharma representatives and regulators, with a view to speed up the marketing authorisation process, especially for ATMP / Advanced Therapies.

Research has been conducted on both the EMA and FDA websites as well as in the literature in order to identify opportunities to interact with these two regulators at the same time. Beyond the possibility to meet representatives of both the EMA and FDA during congresses, a specific procedure called 'EMA-FDA Parallel Scientific Advice' exists and allows to obtain feedback from these two regulators on scientific issues and regulatory requirements during the development phase of a medicine when both the European Union and the United States markets are targeted by medicines' developers for future marketing authorisation applications and potential commercialisations. Initiated as a pilot in January 2005, its success leads to its indefinite extension.

RESULTS

The procedure is clearly defined regarding who can apply, how to submit a request, what are its steps and timetable, and general principles adopted by both the EMA and FDA provide useful guidance to understand this procedure. A 5-year review of this procedure used a Gene therapy medicinal product with an EU and US orphan designation as a case study.

WHO
can request an EMA-FDA Parallel Scientific Advice?

The procedure is generally requested by a medicine developer on a voluntary basis. But the EMA and FDA may also initiate the EMA-FDA Parallel Scientific Advice process in full cooperation with the medicine developer in exceptional circumstances.

The medicine developer can be:

- the "**sponsor**" of an Investigational New Drug Application in the United States
- the "**applicant**" that submits a New Drug Application or Biologics License Application in the United States
- a **potential marketing authorisation applicant** under the marketing authorisation process in the European Union

WHAT
topic for an EMA-FDA Parallel Scientific Advice?

In general:
- Specific scientific or regulatory questions related to the development of a medicinal product for which the sponsor seeks additional guidance or input from both the EMA and the FDA.
- It can be asked only for a specific part of the development

The best candidates for EMA-FDA Parallel Scientific Advice are:
- Important medicinal products (unmet medical needs)
- Medicines developed for indications lacking development guidelines, or with significantly different guidelines from EMA and FDA
- Biosimilars, products with significant clinical safety, animal toxicology, or unique manufacturing concerns that could impede further product development

CONTENT OF REQUEST

A description of the product in development

The product: Haematopoietic stem and progenitor cells (HSPC) transduced ex-vivo by a gene carrying lentiviral vector for treatment of an enzyme deficiency syndrome

Regulatory elements: Orphan designation in US and EU, Ultra-rare population

An explanation of why a discussion with both FDA and EMA would be beneficial

Aim of the request: to ensure regulatory alignment before initiation of the single pivotal trial

EXAMPLE: A GENE THERAPY MEDICINAL PRODUCT AS A CASE STUDY*

Objectives for the meeting

Topics of questions raised on Non-clinical and Clinical aspects
- Overall non-clinical strategy
- Design of a single pivotal Phase 3 study:
- general design principles: single arm design, use of historic controls
- study population
- primary and secondary efficacy endpoints
- composition of historical comparator cohort
- statistical analysis plan

Topics of questions raised on Clinical, and Chemistry, manufacturing and controls (CMC)
- Drug substance manufacturing
- Comparability assessment for new manufacturing process
- Batch analysis and stability data for lentiviral vector use
- Product release specifications
- Potency assay

Topics of questions to the EMA
- Suitability of envisaged evidence generation to demonstrate 'Significant Benefit' in the context of the EU Orphan Designation
- Paediatric development plan

Topics of questions to the FDA
- Considerations on eligibility for Rare Paediatric Disease Product Application

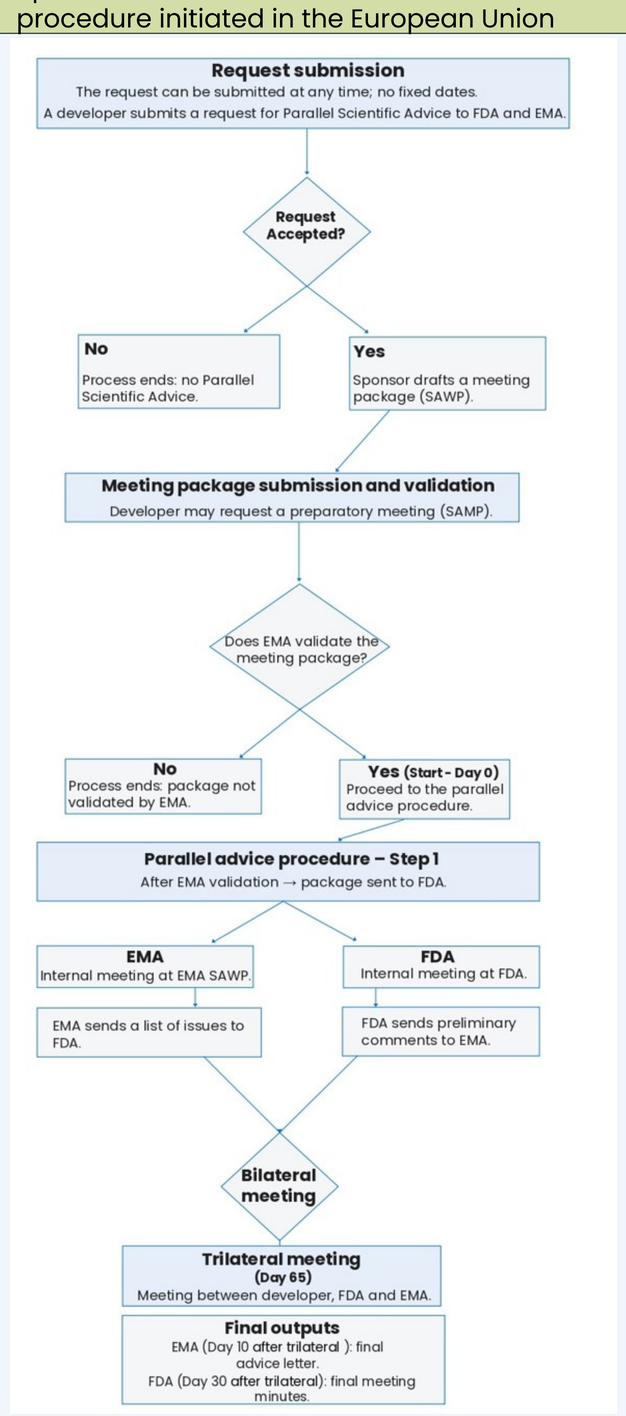
Scope of the request:
- all areas of development: Non-clinical, Clinical, and Chemistry, manufacturing and controls (CMC)
- Focus on CMC requirements and design of a single pivotal clinical study

Specific questions requiring clarification

Explicit consent authorising agencies to share all relevant product information with each other

*Data extracted from Thorsten Vetter, FDA/EMA Parallel Scientific Advice (PSA) – Two case studies, FDA/EMA Parallel Scientific Advice – Webinar, 16 March 2022: https://sbiaevents.com/files2022/FDA-EMA-Webinar-Slides.pdf

HOW?
Steps of the EMA-FDA Parallel Scientific Advice procedure initiated in the European Union



Discussion/Conclusion

The 'EMA-FDA Parallel Scientific Advice' procedure does not guarantee an alignment between EMA and FDA, but it allows to optimize medicines' development and to avoid unnecessary testing due to a deeper understanding of regulatory requirements and an early dialogue with regulators. ATMP, especially where they meet unmet medical needs, appear as good candidates for this procedure.

A 5-year review of this program, conducted by Thor et al., 2023 shows positive views from regulatory staff involved:
- Expansion of their thinking
- Opportunities to discuss how to address common challenges, especially in therapeutic areas with difficult issues and limited experience
- Exploration of alternative or innovative approaches
- Added value to the advice given to the applicant

But there is a low uptake of the program (National Academies of Sciences, Engineering, and Medicine, 2024):
- 37 requests received between 2017 and 2021 (70% accepted)
- Despite interviewees' awareness of the program, uncertainties on its values: non-binding advice, potential for EMA and FDA discordance, timing issues, and concerns on a higher evidence threshold.

In that context, in 2024, a Committee of the National Academies of Sciences, Engineering, and Medicine recommended the FDA, EMA and other stakeholders to conduct an impact assessment of this program and plan for improvement including:
- "Reasons (real and perceived) for continued underuse of the PSA program and address the issues identified;
- Information-gathering on sponsor experience with PSA regarding the practical considerations (e.g., resources, location) for large and small companies to participate in PSA;
- Incentives that encourage use of the PSA program earlier in development (i.e., prior to enrolling patients in trials);
- Metrics for assessing the impact of the PSA program; and
- Criteria and goals for demonstrating improvement of the PSA program with established timeframes over a 5-year period" (National Academies of Sciences, Engineering, and Medicine, 2024)

To date, we have not found any information regarding an ongoing impact assessment of this procedure.

Main references

- EMA & FDA, General principles EMA-FDA parallel scientific advice (human medicinal products), July 2021
- EMA, EMA-FDA Parallel Scientific Advice (PSA) Timetable
- FDA, Procedures for Parallel Scientific Advice with European Medicines Agency (EMA), Center for Biologics Evaluation and Research, SOPP 8001.6, V.5, Effective Date, 12 January 2023
- FDA & EMA Webinar, FDA-EMA Parallel Scientific Advice (PSA) Program and Event Material, March 16, 2022
- National Academies of Sciences, Engineering, and Medicine. 2024. Regulatory processes for rare disease drugs in the United States and European Union: Flexibilities and collaborative opportunities. Washington, DC: The National Academies Press. https://doi.org/10.17226/27968; Chapter 5, FDA and EMA Collaboration, p. 223.
- Thor S, Vetter T, Marcal A, Kweder S. EMA-FDA Parallel Scientific Advice: Optimizing Development of Medicines in the Global Age. Ther Innov Regul Sci. 2023 Jul;57(4):656-661. doi: 10.1007/s43441-023-00501-9.