

White Paper: EuropaBio Position & Policy Recommendations to support EU ATMP Innovation

Europe has been a pioneer in the field of Advanced Therapy Medicinal Products (ATMPs) in terms of their development, authorisation, and regulation, thereby supporting patient access to these life-changing therapies. Between Jan. 2014 - Jun. 2019, 323 investigational clinical trials were initiated in Europe. However, this is less than half of what was observed in North America and Asia, with the number of new clinical trials increasing by <2% in Europe versus 36% and 28% in North America and Asia, respectively.¹ To ensure the EU remains a leader in ATMP innovation, this paper outlines and elaborates EuropaBio's position and policy recommendations to the European Commission (EC) across three key focus areas.

Clinical Trial Requirements

There is significant clinical trial complexity in the EU owing to Member States own interpretation of Clinical Trial Authorisation (CTA) legislation. This complexity creates confusion for ATMP developers and can lead to significant delays of planned trials, decreasing the attractiveness of conducting such trials in the EU. The upcoming Clinical Trial Regulation (CTR) (EU) No 536/2014 aims to promote the implementation of a harmonised CTA dossier and review timelines adopted by all Member States. However, EuropaBio is concerned that ATMP products will fall out of the CTR process owing to unrealistic review and response timelines as well as a submission portal that is not fit for purpose for ATMPs. As such, it is recommended that the EC and Clinical Trials Facilitation and Coordination Group (CTFG) build upon the learnings from the Voluntary Harmonised Procedure (VHP) for clinical trials and conduct ATMP-specific pilots to identify and resolve potential issues prior to wide-spread rollout of the CTR. Furthermore, enhanced centralised scientific advice procedures that allow for rapid advice on par with procedures in other jurisdictions, specifically the US, are requested to support timely EU involvement in global development programmes.

Genetically Modified Organism (GMO) Requirements

ATMPs that consist of or contain GMO are required to undergo additional approval procedures by GMO competent authorities in each Member State prior to CTA. This regulatory framework was not designed for pharmaceuticals and is not standardised across Member States resulting in developers undergoing multiple, inefficient and redundant procedures which are costly and can lead to significant delays to development programs. A single, networked approach conducted in parallel to CTA assessments is desired with the upcoming CTR providing an opportunity for the EC and CTFG to work with GMO authorities to achieve this. EuropaBio would like to collaboratively explore with the EC whether GMO requirements are appropriate for medicines given the current state of knowledge as well as how duplication between medicines and environmental agencies can be avoided to ensure optimised processes are in place to handle the increasing number of these products under development.

Optimised Evidence Requirements Including Real World Evidence (RWE)

It is often not possible to conduct large, randomised controlled clinical trials for ATMPs leading to uncertainty regarding their authorisation and reimbursement. However, RWE can be leveraged to complement ATMP clinical trial data and provide higher levels of confidence at the time of pre- and post-Marketing Authorisation (MA) decisions. There are no mature and relevant guidelines worldwide that clearly define the scope of application of RWE to drug development and there is therefore an opportunity for the EU to become a leading voice in defining its optimal use. EuropaBio recommends that a permanent working structure and information exchange platform is developed between the European Medicines Agency (EMA), national Health Technology Assessment (HTA) bodies and payers with the intention to collect and utilise "universal evidence," i.e. data that supports the different needs of all stakeholders. This group would be tasked with initiating reviews and demonstration projects that ultimately allow for guidelines to be developed for the systematic integration of RWE to enhance drug development, authorisation and reimbursement processes.

¹ Alliance for Regenerative Medicines. Clinical Trials in Europe: Recent Trends in ATMP Development. 1-13 (2019).

1. Clinical Trial Requirements

1.1. Background Information

Regulation 1394/2007 requires that ATMPs undergo a centralised Marketing Authorisation Application (MAA) where safety and efficacy data generated through clinical trials is evaluated by the EMAs Committee for Medicinal Products for Human Use (CHMP) and its Committee for Advanced Therapies (CAT). A positive risk:benefit opinion is required from the CAT and CHMP to be granted MA by the EC. However, approval of an ATMP developer's CTA occurs independently at a national level by the National Competent Authority (NCA) of a Member State² whose own interpretation of legislation has resulted in significant diversity in clinical trial approval timelines, data requirements and procedures among EU Member States. This multi-layered regulation was the most frequently cited challenge experienced by ATMP developers in a recent survey.³

1.2. EuropaBio Position and Policy Recommendations

Addressing Divergence between Member States

EuropaBio is supportive of the 2019 draft Guideline on quality, non-clinical and clinical requirements for investigational ATMPs in clinical trials as it provides developers with clarification on how to design their development programme. EuropaBio also supports CTR (EU) No 536/2014 which aims to see a harmonised CTA dossier and review timelines adopted by all Member States, with the assessment facilitated through an online EU-wide Clinical Trial Portal. However, EuropaBio is concerned that ATMP products will fall out of the CTR process owing to:

- Differences in ATMP review between Member States,
- Unrealistic response timelines, for example, it is likely that many ATMP developers will be unable to provide answers in 12 days given the extent of questions in some Member States, and
- The portal not being fit for purpose, for example, it seems it has not been designed to accept applications with complex innovative designs that are frequently used to accelerate the development of ATMPs and it is not compatible with what is currently expected for ATMPs that consist of or contain GMO.

EuropaBio recognises that the CTFG is overseeing several pilots in Member States, including participation in Voluntary Harmonised Procedure (VHP)-plus initiatives where Ethics Committees also take part in the harmonised multi-country assessment, in support of the transition to the new Clinical Trial Regulation EU 536/2014.⁴ However, apart from the trials taking place in Denmark and Belgium, it is not clear whether ATMPs are included in these pilots. As such, EuropaBio recommends that the EC and CTFG assess ATMP developer's experience using the VHP and VHP-plus and initiate ATMP-specific pilots including countries that have a high degree of ATMP clinical trial experience, such as Germany, to identify and resolve potential issues with the different stakeholders prior to wide-spread rollout of the CTR.

² Detela, G. & Lodge, A. EU Regulatory Pathways for ATMPs: Standard, Accelerated and Adaptive Pathways to Marketing Authorisation. *Molecular Therapy - Methods and Clinical Development* **13**, 205–232 (2019).

³ ten Ham, R. *et al.* Challenges in Advanced Therapy Medicinal Product Development: A Survey among Companies in Europe. *Molecular Therapy - Methods and Clinical Development* **11**, 121–130 (2018).

⁴ Clinical Trials Facilitation and Coordination Group. European Union Member States national pilot projects and participation in VHP-plus in support of the transition to the new Clinical Trial Regulation EU 536/2014 (2019). Available at: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-about_HMA/Working_Groups/CTFG/ (Accessed: 6th February 2020).

Scientific Advice

Rapid scientific advice is the best way to guide and validate development plans in a timely manner. However, the most rapid advice routes, namely through NCAs, have historically resulted in inconsistent and occasionally conflicting advice owing to varying levels of authority's ATMP familiarity.⁵ Centralised scientific advice offering consistent pan-EU feedback is available, but typically takes 4 months or longer to solicit compared to 60 days in the US. This timeframe is not adept to meet the needs of ATMP developers, particularly SMEs with limited resources who cannot afford to wait for this EU opinion to pursue development.⁶ As such, many trials begin without EU input which hinders product development and delays patient access. The PRIME scheme is viewed as highly valuable as it allows for earlier engagement with regulators and guidance from a CAT rapporteur, but current eligibility criteria mean that some developers cannot access the scheme at a time when it would be most useful and the mechanism for soliciting scientific advice is still via the centralised procedure.

EuropaBio is supportive of the new pilot launched by the EU Innovation Network on 1 February 2020 that allows for Simultaneous National Scientific Advice (SNSA) to be obtained from two NCAs within one application, as this coordinated approach may provide an opportunity to resolve potentially conflicting opinions between NCAs, increase alignment among NCAs on different regulatory positions and/or requirements as well as provide feedback to developers earlier.⁷ However, while the program will allow for early identification of issues that require centralised advice, developers are still required to apply for centralised advice independently and this therefore does not address the long wait-times for obtaining feedback. To become competitive with other jurisdictions such as the US who offer single-agency advice in significantly shorter timelines than in the EU, short-, mid- and long-term recommendations are listed in Table 1.

Table 1: EuropaBio policy recommendations relating to improving scientific advisory services

| Timeframe | Recommendations |
|-------------------|--|
| Short-Term | <ul style="list-style-type: none"> • Rapid Advice: create a mechanism through which the NCAs or SNSA participants can act as gatekeepers and triage critical questions from developers to the CAT for rapid response. This would accelerate development timelines as well as increase NCAs knowledge-base, gradually alleviating pressure from the CAT. Furthermore, FAQs could be captured and shared across NCAs for increased knowledge-sharing and consistency • Enhanced Paediatric Advice: create a working structure for enhanced communication between members of the Paediatric Committee (PDCO) and CAT to facilitate rapid ATMP development in paediatric indications • Optimisation of PRIME scheme: allow eligibility for any developer on the basis of non-clinical data when accelerated development is envisaged, for example, a |

⁵ ten Ham, R. *et al.* Challenges in Advanced Therapy Medicinal Product Development: A Survey among Companies in Europe. *Molecular Therapy - Methods and Clinical Development* **11**, 121–130 (2018).

⁶ Alliance for Regenerative Medicine. Position on possible solutions to foster development and expand patient access for Advanced Therapy Medical Products in Europe.

⁷ Federal Medicines Agency for Medicines and Health Products. Pilot project on simultaneous national scientific advice starts 1 February 2020 (2020). Available at:

https://www.famhp.be/en/news/pilot_project_on_simultaneous_national_scientific_advice_starts_1_february_2020 (Accessed: 4th February 2020).

single Phase 1/2 study is proposed to support the MAA. Additionally, leverage the designated CAT rapporteur to obtain centralised advice in a more timely manner

Mid-term

- **EMA-FDA Collaboration:** increase transparency around development plan requirements to help drive future alignment
- **Expert Group Formation:** assign a CAT rapporteur to guide the entire development process of a product with a ‘one-stop-shop’ session at the start attended by members of a relevant, dedicated multi-disciplinary (possibly multi-agency) team (CMC, non-clinical, clinical, paediatric) to align on one clinical development program

Long-term

- **EMA-FDA Collaboration:** build upon the current EMA FDA parallel scientific advice scheme by launching an ATMP-specific pilot with streamlined mutual recognition processes to ease multi-national trials, reduce unnecessary replication and overall timelines as well as ensure patients gain timely access on a global scale

2. Genetically Modified Organism (GMO) Requirements

2.1. Background Information

In the case of ATMPs consisting of or containing GMOs, an additional approval for the environmental and biosafety aspects of the use and release of the GMO is required by the GMO competent authorities who often operate independently of the health authorities. Local interpretation of GMO legislation that was not developed specifically for medicinal products has resulted in highly fragmented procedures across the EU in terms of the classification, requirements and timings for GMO applications and approvals. As such, developers have found adherence to GMO legislation as resource intensive and confusing with little apparent patient, product or environmental benefit.⁸ Additionally, several rounds of reviews can result in delays of up to 12 months to planned CTAs in some cases.⁹ Without action, these barriers can disincentivise ATMP developers to conduct trials in the EU with ATMPs consisting or containing GMOs, affecting patients and EU competitiveness.

2.2. EuropaBio Position and Policy Recommendations

EuropaBio met with the EC in 2016 where recommendations were mutually exchanged to improve ATMP clinical trials consisting of or containing GMOs. EuropaBio acknowledges the progress made by the EC and Member States in terms of reducing the complexity of GMO requirements with the recent introduction of 'Common Application Forms' and 'Good Practice Documents' for human cells genetically modified and in-vivo gene therapy utilising AAV clinical vectors.¹⁰ However, these documents do not cover the full range of GMO applications and it has come to EuropaBio's attention that Member States who have endorsed the use of common application forms do not necessarily utilise them meaning that disparities in evidence submissions and evaluation remain. A single, networked approach ideally offering GMO assessment in parallel to CTAs is desired with the upcoming CTR providing an opportunity for the EC, CTFG and GMO authorities to collaborate to achieve this. EuropaBio would like to collaboratively explore ways forward for the future of these products with the EC to ensure an efficient and streamlined process is in place to handle the increasing number of these products in development:

1. Assess whether GMO requirements are appropriate for medicines given the current state of knowledge. For example, exclusion criteria could be developed where prior in-human experience (including outside of the EU) has proven that the ATMP poses no risk to the environment or where the product class has been reviewed by the GMO authorities as no risk.
2. The potential for centralised decision-making on GMOs, to avoid divergence between Member States as well as duplication between medicines and environmental competent authorities, given the ongoing EU work on 'Pharmaceuticals in the Environment'¹¹ and experience with GMO harmonisation achieved to date.

⁸ ten Ham, R. *et al.* Challenges in Advanced Therapy Medicinal Product Development: A Survey among Companies in Europe. *Molecular Therapy - Methods and Clinical Development* **11**, 121–130 (2018).

⁹ ARM, EBE, EFPIA & EuropaBio. Possible solutions to improve the European regulatory procedures for clinical trials with Advanced Therapy Medicinal Products consisting of or containing Genetically Modified Organisms. 1–6 (2017).

¹⁰ European Commission. Genetically Modified Organism (GMO) Requirements for investigational products (2019). Available at: <https://ec.europa.eu/health/human-use/advanced-therapies> (Accessed: 16th October 2019).

¹¹ European Commission. Pharmaceuticals in the Environment (11 March 2019). Available at: https://ec.europa.eu/commission/news/pharmaceuticals-environment-2019-mar-11_en (Accessed: 9th March 2020)

3. Optimised Evidence Requirements Incl. Real World Evidence (RWE)

3.1. Background Information

Randomised Controlled Trials (RCTs) are considered the “gold standard” to generate robust evidence that can be used to assess a drug’s safety and efficacy. However, these are difficult to conduct in the case of ATMPs owing to:

- Smaller patient populations often necessitating the use of single-arm trials,
- A lack of alternative treatments often resulting in difficulty identifying appropriate comparators,
- The potential for randomisation to a control group considered unethical, and
- The use of surrogate outcomes rather than clinical outcomes, which are lengthy to acquire in some indications, enabling shortened trials and accelerated patient access once efficacy is established.¹²

RWE stems from the correct and adequate analysis of real-world data (RWD) which encompasses sources such as pooled clinical trial data and observational studies, omics-related datasets, electronic health records, registry and claims data, off-label or compassionate use data as well as data collected from mobile devices and wearables.¹³ This RWE can be leveraged to complement the evidence generated from ATMP clinical trials and provide higher levels of confidence at the time of pre- and post-MA decisions. For example, natural history data can serve as an external control in the case of single-arm trials to facilitate regulatory decisions, but also HTA processes which require sufficient evidence to make cost:benefit evaluations that determine reimbursement. However, the required standards to produce RWE that is acceptable for downstream decision-making have not yet been fully defined with clarification around relevant and reliable (data quality) RWD sources required as well as alignment on appropriate methods for transforming RWD into RWE and evidentiary standards for RWE acceptability.

3.2. EuropaBio Position and Policy Recommendations

EuropaBio is supportive of the HMA-EMA joint Big Data Task Force (BDTF) which aims to support regulators and stakeholders seize the opportunity for data-driven, evidence-based, robust decision-making that will underpin the development, authorisation and on-market safety and effectiveness monitoring of medicines in a rapidly evolving data and analytics landscape.¹⁴ In particular, the 10 priority recommendations which include building an EU data platform (**Data Analysis and Real World Interrogation Network -DARWIN**) by 2023, establishing guidelines for an EU RWE framework to capture high quality and representative data, developing skills and infrastructure to process this data, and launching a ‘Big Data Learnings Initiative’ to collect data that can be used to develop guidelines is viewed as highly valuable.

While increased dialogue with HTA bodies and payers is envisioned as part of a ‘Stakeholder Implementation Forum’ by the BDTF, EuropaBio believes that a permanent working structure and information exchange platform between these stakeholders would allow for the collection of “universal evidence,” i.e. defining a

¹² Jönsson, B. *et al.* Advanced therapy medicinal products and health technology assessment principles and practices for value-based and sustainable healthcare. *European Journal of Health Economics* **20**, 427–438 (2019).

¹³ Center for Drug Evaluation, NMPA. Key considerations in Using Real-World Evidence to Support Drug Development (Draft for Public Review). 1-17 (2019).

¹⁴ Heads of Medicines Agency and European Medicines Agency. HMA-EMA Joint Big Data Taskforce Phase II report: ‘Evolving Data-Driven Regulation.’ 1-61 (2020).

dataset that supports the different needs of all stakeholders.¹⁵ For example, the ‘Parallel Consultation’ procedure launched in 2017 has been successful as it allows for joint regulatory and reimbursement feedback from the EMA and the European Network for Health Technology Assessments (EUnetHTA), allowing for mutual understanding of the evidence generation constraints faced by all stakeholders and subsequent alignment on acceptable evidence generation plans from an early stage of product development.¹⁶ The Parallel Consultation procedure is limited by resource availability, but a similar concept can be extrapolated to the proposed permanent working structure to facilitate immediate integration of learnings to date and provide access to life-changing products to patients sooner. Short- and mid-term tasks that this working structure need to focus on are outlined in Table 2.

Table 2: EuropaBio policy recommendations relating to the use of RWE to aid drug development and decision-making

| Timeframe | Recommendations ¹⁷ |
|-------------------|--|
| Short-Term | <ul style="list-style-type: none"> • Parallel Consultation Optimisation: conduct reviews of the parallel consultation procedure to demonstrate the value of early engagement as well as the value of convergence across different decision makers. Specific knowledge can be captured through these reviews to be made widely available and eventually distilled into joint guidance. • ATMP HTA Framework: collaborate with EU and international stakeholders to agree on standards for RWD quality and RWE methodology and evidentiary standards to incorporate natural history or big data and/or enhanced economic modelling into current HTA frameworks as well as align on post-approval data collection • Demonstration Projects: conduct RWE pilot programs to increase knowledge, capacity and confidence levels in RWE submissions and use. Such projects could form the basis for regulatory and reimbursement guidelines on appropriate use of RWE and cover different ATMP scenarios such as pragmatic clinical trials, single-arm trials, trials making use of surrogate endpoints, etc. • RWE Best Practice: continue to collaborate with stakeholders in EU and internationally to host workshops that share best practices in terms of design, collection, validation and appropriate use of RWE. |
| Mid-term | <ul style="list-style-type: none"> • Strategic Initiative: develop guidelines to integrate systematic use of RWE from the DARWIN database to support drug development, regulatory and reimbursement decision-making. |

¹⁵ European Medicines Agency. Optimising evidence incl. RWD for decision making and communication. *EMA’s Regulatory Science Strategy to 2025 – Human Stakeholder Workshop*, 1-10 (2019).

¹⁶ European Medicines Agency. Guidance for Parallel Consultation EMA/410962/2017.

¹⁷ European Medicines Agency. Promote use of high-quality real-world data (RWD) in decision-making. *EMA’s Regulatory Science Strategy to 2025 – Human Stakeholder Workshop*, 1-18 (2019).