
Alliance for Regenerative Medicine
MEETING THE MOMENT
HARNESSING THE FULL POTENTIAL OF ATMPS FOR EUROPEAN PATIENTS

BACKGROUND

Modernising EU policy and legislation to reflect the unique nature and promise of ATMPs is critical if EU patients are to benefit from their transformative impact. It is also necessary if the EU aspires to harness its world-class research and re-establish its position as a leader in innovation.

Europe is at a crossroads — it is imperative to act now. After a fast start, the competitiveness of the EU in the ATMP sector has been declining. The number of therapeutic developers, clinical trials, and investment is stagnating in the EU--a trend in stark contrast with other regions of the world. Patients in Europe cannot afford to miss out on treatments which the European Commission itself has called "milestones of major progress" in the Pharmaceutical Strategy for Europe.

A total of 23 ATMPs have been granted Marketing Authorisation by the European Medicines Agency in 20 different therapy areas to date. With over 2,000 clinical trials ongoing, we expect this number to grow considerably over the coming years to the benefit of European patients. However, to unleash this potential, it will be crucial that the implementation of the EU Joint Clinical Assessment (part of the EU HTA Regulation) and the revision of the EU pharmaceutical legislation create a supportive framework.

What are ATMPs?

Advanced therapy medicinal products (ATMPs) are medicines based on genes, tissues and/or cells. They offer ground-breaking new opportunities by addressing the root cause of disease. ATMPs differ fundamentally from conventional medicines with their ability to transform the lives of patients and families through halting disease progression or modifying the trajectory of the disease.

Unlike conventional medicines which generally require long term administration and treat disease symptoms, ATMPs are typically administered once- or twice-only and provide sustained long-term benefits.

The Challenge

21st Century science will not reach patients if 20th Century policies and legislation are not updated to reflect the specificities of ATMPs.

MAKE THE EU JOINT CLINICAL ASSESSMENTS WORK FOR ATMPS

As part of the implementation of the EU HTA Regulation, from January 2025, ATMPs will undergo a new EU-coordinated Joint Clinical Assessment (JCA) to evaluate their added clinical benefit. The outcome of JCAs will then be used by Member States when finalising national HTA processes and in taking pricing and reimbursement decisions.

The Alliance for Regenerative Medicine is supportive of an EU JCA as we believe that, if appropriately designed and implemented, it will help accelerate patient access to innovative medicines by reducing duplicative assessments at the country level. However, to achieve this goal it will be essential that the JCA takes into account the specific characteristics of ATMPs and doesn't merely constitute an additional administrative hurdle which further delays products becoming available for patients.

Existing HTA methods were originally developed to assess and appraise conventional medicines and did not anticipate the characteristics and transformative benefit of ATMPs. While, typically, Randomised Controlled Trials (RCT) with large sample sizes are required to detect small treatment effects in relative short time periods, they are often not a feasible and appropriate approach for the assessment of ATMPs. Indeed, very often ATMPs can be studied only in non-comparative clinical trials, their treatment effect is very large, and the duration of effect is expected to exceed the length of clinical trials by several years, if not for decades. Furthermore, often ATMPs are authorised via accelerated procedures, in light of their significant potential, which further exacerbates the developer's ability to collect compelling data to substantiate assessment of full value.

Therefore, there is a need to design JCA methods that are fit-for-purpose for ATMPs so that their potential value over the longer term can be captured, therefore enabling them to reach patients. The Alliance for Regenerative Medicine believes that the draft EU JCA methods developed by the EUnetHTA 21 consortium are not appropriate for ATMPs and should be changed substantially.

***Call to Action**: We call on the EU HTA Coordination group, the European Commission and Member States to engage with the Alliance for Regenerative Medicine and relevant stakeholders to identify appropriate methods for JCA of ATMPs.*

The primary focus of this effort should be on developing methods for indirect comparisons in the absence of RCT evidence, as a valid approach for assessing clinical benefit of ATMPs. This should be complemented by real world evidence to best address uncertainty about long-term effectiveness. Furthermore, we recommend that health technology developers, representatives of patients and health care professionals be involved in an iterative dialogue throughout the JCA process.

SUPPORT EU COMPETITIVENESS IN THE ATMP SECTOR WITH THE REVISION OF THE PHARMACEUTICAL LEGISLATION

While several aspects of the revision of the EU pharmaceutical legislation are important for the ATMP sector, the Alliance for Regenerative Medicine would like to draw attention to two specific areas which are key factors for the competitiveness of the EU in the sector.

Restrict and harmonise the use of the Hospital Exemption

The existing EU legislation allows the provision of an ATMP without a marketing authorisation via the Hospital Exemption (HE). This exemption should only be used under exceptional circumstances of unmet need, when no other treatment options are available for a given indication (e.g. no authorised therapies exist or no ongoing clinical trials in which the patient could be enrolled).

Due to the investigational / experimental nature of HE products, the evidence required to obtain an HE license is not comparable to an EMA authorised ATMP. As such, these products should only be used in exceptional circumstances in the interest of patient safety and quality of care. Most importantly, in the best interest of patients, it is crucial that the HE is not used as an alternative to the EMA process for Marketing Authorisation, including clinical trials. The reason being that, if used as an alternative deregulated pathway, it would jeopardise the ongoing and planned efforts to develop the clinical trial evidence needed to fulfil EU regulatory and HTA requirements.

Currently, there are great variations in the interpretation of the HE across the EU. These different interpretations have led to situations where the HE is inappropriately applied to a large number of patients in some Member States, including when a marketed ATMP has been authorised by EMA for the same indication, therefore contradicting the EU definition of HE. Using the HE in situations where patients could be treated with approved ATMPs results in a two-tiered regulatory system that not only creates different quality and safety standards for patients, but also undermines the existing EU ATMP regulatory system, worsens the EU's competitiveness in the sector, and puts the functioning of the EU internal market at risk.

***Call to action**: As part of the revision of the EU general pharmaceutical legislation, the Alliance for Regenerative Medicines calls on the European Commission to:*

- *Maintain the HE as an "exemption", allowing only the provision of experimental treatments to patients without other options and on a 'non-routine' basis.*
- *The legislation should clearly specify that the HE could not be used when an authorised ATMP is available for a given indication or in case the patient could have access to an investigational medicine in an ongoing clinical trial. Furthermore, the legislation should clearly indicate that the HE is not applicable in case of large-scale, industrial production.*
- *Ensure a consistent interpretation of HE in the EU Member States, by providing clear definitions (e.g. on the concept of non-routine basis).*
- *Introduce a mandatory registry under EMA's supervision with publicly accessible information relating to ATMPs produced under HE to ensure greater transparency on the use of the HE across Member States and to allow greater scrutiny and assurance that the system is being used as intended by the EU legislation.*

Exempt ATMP clinical trials from GMO application

EU legislation on Genetically Modified Organisms (GMOs) was designed primarily for agricultural applications to protect food consumers and the environment. Nevertheless, ATMPs that consist of or contain GMO must comply with the regulations.

Currently, in the EU, clinical trials conducted with products containing or consisting of GMOs must receive a GMO approval in each of the countries in which the clinical trial is conducted. As the GMO rules have been implemented differently across the EU, complying with these requirements is complex, especially when clinical trials are conducted in several Member States.

These requirements lead to prolonged approval timelines and have been a contributing factor to the decline of ATMP clinical trials in Europe compared to other regions. This is detrimental to EU patients since it delays their access to transformative medicines.

***Call to Action:** The Alliance for Regenerative Medicine calls for a derogation from GMO approval for clinical trials with investigational ATMPs containing or consisting of GMOs, since their environmental risk is most often negligible. Such an approach is in line with the derogation from GMO requirements permitted during the pandemic for the development of Covid vaccines and therapies.*

ABOUT THE ALLIANCE FOR REGENERATIVE MEDICINE

The Alliance for Regenerative Medicine (ARM) is the leading international advocacy organisation dedicated to realising the promise of advanced therapy medicinal products (ATMPs). ARM promotes legislative, regulatory, reimbursement and manufacturing initiatives in Europe and internationally to advance this innovative and transformative sector. In its 13-year history, ARM has become the global voice of the sector, representing the interests of 475+ members worldwide and 85+ members across 15 European countries, including small and large companies, academic research institutions, major medical centres and patient groups. www.alliancerm.org