

13 November 2020

Call for more effective EU regulation of clinical trials with Advanced Therapy Medicinal Products consisting of or containing Genetically Modified Organisms

Executive Summary

Advanced Therapy Medicinal Products (ATMPs), such as gene therapies that consist of or contain Genetically Modified Organisms (GMOs), need to comply with the European Union (EU) GMO legislation before they can be used in clinical trials. Complying with GMO requirements is complex, varies across the EU, and is leading to delays in clinical trials with ATMPs. This makes the EU less attractive than other regions for conducting clinical trials with gene therapies. This is detrimental to EU patients since their access to these transformative, potentially curative medicines is delayed.

Despite recent initiatives coordinated by the European Commission (EC) to facilitate and reduce discrepancies across the EU regarding the application of the GMO requirements, it remains particularly difficult to conduct multi-centre clinical trials with ATMPs containing or consisting of GMOs involving several EU Member States. The recent decision to temporarily exempt potential COVID-19 treatments and vaccines from some provisions of the GMO requirements is a clear recognition of such complexities and delays to clinical development.

The Alliance for Regenerative Medicine (ARM), the European Federation of Pharmaceutical Industries and Associations (EFPIA), and the European Association for Bioindustries (EuropaBio), call upon the European Commission, together with national regulatory authorities, to facilitate access to ATMPs containing or consisting of GMOs in the EU. Major simplification and acceleration of the GMO assessment process will make Europe more attractive as a place for clinical development and will allow more rapid European patients' access to these potentially life-saving medicines.

To meet these objectives, it is proposed that an exemption scheme should be implemented for ATMPs undergoing clinical trials.

In the framework of the new EU Pharmaceutical Strategy, we urge the European Commission to use its right of initiative to put forward a legislative proposal to this effect.

1. Background and problem statement: The EU GMO legislation delays clinical trials and patient access to potentially life-saving therapies.

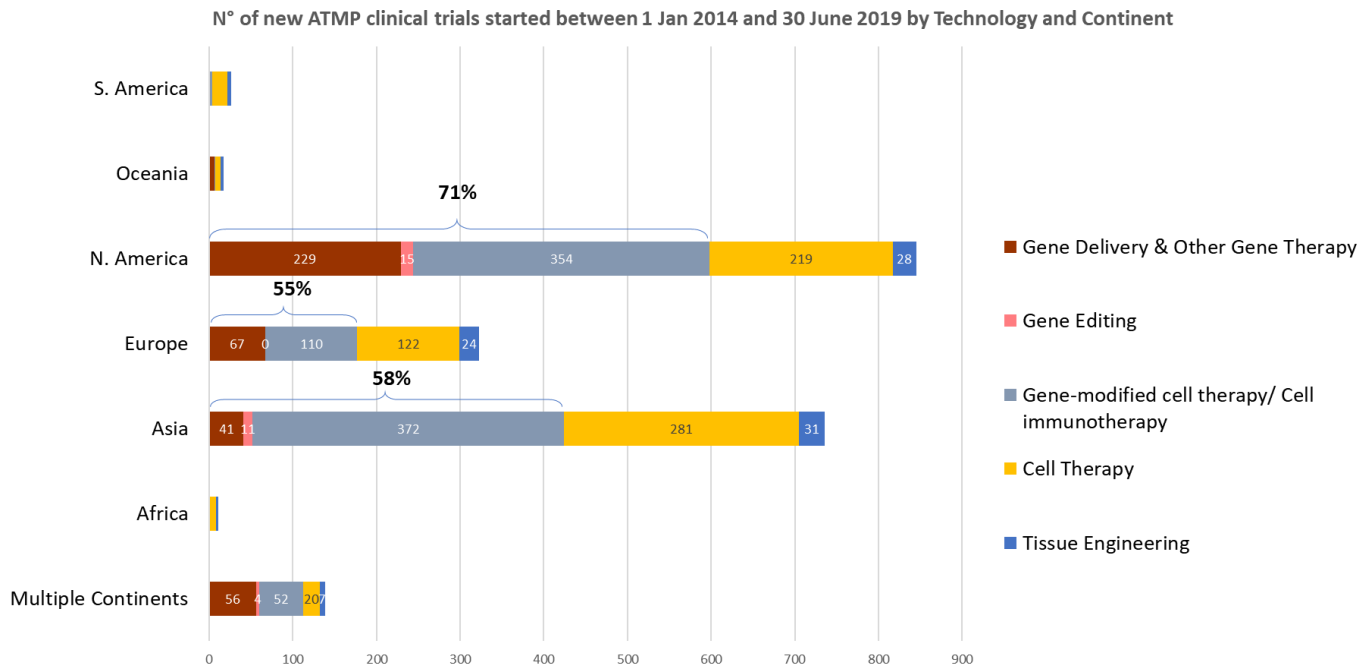
Advanced therapy medicinal products are innovative medicinal products which have the potential to bring highly transformative value to patients, including potential cures, by either correcting the underlying cause of their disease (e.g. a genetic defect) or by modifying a function in the body to cure or significantly ameliorate their disease. Some ATMPs, such as gene therapies, consist of or contain GMOs. Even though the EU legislation on GMOs was drafted and adopted primarily with agricultural applications (plant GMOs) in mind with a goal to protect food consumers and the environment, the authorisation procedure for clinical trials with investigational ATMPs requires additional steps to comply with the GMO legislation.

The EU legislation prescribes that clinical trials with investigational products containing or consisting of GMOs comply with either Directive 2001/18/EC on the deliberate release into the environment of GMOs or with Directive 2009/41/EC on the contained use of GMOs. Such requirements come on top of the requirements for authorisation of clinical trials laid down in the Clinical Trial Directive 2001/20/EC and the Clinical Trials Regulation (EU) No 536/2014 which repeals the Clinical Trial Directive and is expected to be implemented at the end of 2021.

Since both GMO Directives are transposed with variations and applied in different manners by national authorities in each Member State, decisions made under the GMO legislation are not applied consistently, leading to different decisions across the EU. Moreover, since the two regimes (GMO and Clinical Trials legislations) both apply, without defining a *modus operandi* for how they should interoperate, different approaches may be taken by different Member States: either applying the GMO approval regime before, or in parallel with the application to national health authorities.

Data show that Europe is less successful than other regions in attracting new clinical trials with ATMPs, in particular with gene therapies

The ARM report "[Clinical Trials in Europe: Recent Trends in ATMP Development](#)" of October 2019 signalled that Europe has become less competitive than other regions of the world in attracting new ATMP clinical trials, particularly clinical trials involving GMOs. Whilst the number of new ATMP clinical trials has significantly grown over a 4-year period (2014-2018) on a global scale (+32%), with notable growth in North America (+36%) and Asia (+28%), this increase has not been observed in Europe where the number of new clinical trials remained constant over the time period analysed (<2%). The proportion of new gene therapy (gene editing, gene therapy and gene modified cell therapy) clinical trials is also considerably lower in Europe than in other regions (see Figure below). The complexity of GMO requirements for clinical studies leading to prolonged approval timelines exacerbates Europe's lack of attractiveness and is a major cause for this lower number.



Source: ARM report "[Clinical Trials in Europe: Recent Trends in ATMP Development](#)"¹

Europe's relative lack of appeal with ATMP developers may become more pronounced as the number of new gene therapies is rapidly growing. As of 30 June 2020, on a total of 1078 on-going clinical trials with ATMPs on a global scale, 830 (77%) are classified as gene therapies. Having insufficient clinical development of advanced therapies in Europe is a missed opportunity and a major issue that needs to be addressed, with patients having limited early access to these therapies, physicians having limited experience with the products when they come to market and marketing authorisation applications with limited data on EU patients.

GMO requirements for investigational medicines are more stringent and complex in Europe than in the US

The most popular country for carrying out clinical trials with gene therapies is, by far, the USA. Clinical studies using GMOs in the United States are not subject to the same requirements as those typically encountered in Europe.² The US Center for Biologics Evaluation and Research released non-binding recommendations on cases wherein the GMO environmental risk assessment is not needed for gene therapies, vectored vaccines, and related recombinant viral or microbial products.³ A claim of 'categorical exclusion' ordinarily applies to clinical studies, allowing an exemption from the requirements for an environmental assessment under 21 CFR 25.31(e) for investigational new drugs (INDs).⁴

Gene therapies based on genome editing techniques are currently also considered GMOs

On 25 July 2018, the Court of Justice of the European Union decided that organisms obtained by the new techniques of directed mutagenesis are considered GMOs and are, therefore, subject to the obligations laid down by the GMO Directive.⁵ Even though the background of the Court ruling was an action brought in the context of crops used in agriculture, i.e. the main products concerned by the GMO legislation, the ruling

implies that gene therapies using genome editing techniques are also considered as GMOs under EU legislation.

This decision differs from the current thinking and GMO-related expectations outside Europe.

A few months after the ruling, the European Commission's Scientific Advice Mechanism ([SAM](#)) Group of Chief Scientific Advisors published a statement providing a scientific perspective on the regulatory status of products derived from gene editing, and the implications for the GMO Directive.⁶ The advisors conclude that the GMO Directive should be revised *"to reflect current knowledge and scientific evidence, in particular on gene editing and established techniques of genetic modification"*.

Gene therapies using genome editing technologies, such as CRISPR-Cas9 or TALENs, have the potential to radically transform the standards of care for patients who currently lack treatment options. While the number of clinical trials based on gene therapies using genome editing technologies is now surging⁷, the ruling of the EU Court of Justice may inadvertently delay access to effective new treatments, also entailing a negative impact on the research and innovation landscape in Europe.

Recently, EU authorities have recognized that the EU GMO legislation is responsible for delays in clinical trials

The fact that the GMO legislation causes delays in the development of novel medicines in the EU has been confirmed by the EU's recent actions to tackle the COVID-19 pandemic. The [EU strategy for COVID-19 vaccines](#) acknowledges that *"[t]here is considerable variety across Member States in the national requirements and procedures implementing the GMO Directives used to assess environmental risks of clinical trials of medicinal products that contain or consist of GMOs. This is likely to cause significant delay, particularly for multi-centre clinical trials in several Member States"*.

To accelerate development and access to COVID-19 treatments or vaccines, the EU has adopted Regulation (EU) 2020/1043 to temporarily exempt investigational medicinal products (IMPs) for human use containing or consisting of GMOs to treat or prevent COVID-19 from complying with some provisions of the GMO legislation.⁸

Recitals (8) and (9) of Regulation (EU) 2020/1043 read as follows:

"(8) Experience shows that, in clinical trials with investigational medicinal products containing or consisting of GMOs, the procedure to achieve compliance with the requirements of Directives 2001/18/EC and 2009/41/EC as regards the environmental risk assessment and consent by the competent authority of a Member State is complex and can take a significant amount of time.

(9) The complexity of that procedure increases greatly in the case of multi-centre clinical trials conducted in several Member States, as sponsors of clinical trials need to submit multiple requests for authorisation to multiple competent authorities in different Member States in parallel. In addition, national requirements and procedures for the environmental risk assessment and written consent by competent authorities for the deliberate release of GMOs under Directive 2001/18/EC vary greatly from one Member State to another. Whereas in some Member States a single request for authorisation concerning the conduct of the clinical trial and the GMO aspects can be submitted to a single competent

authority, in other Member States parallel requests need to be submitted to different competent authorities. Furthermore, some Member States apply Directive 2001/18/EC, others apply Directive 2009/41/EC and there are Member States that apply either Directive 2009/41/EC or 2001/18/EC depending on the specific circumstances of a clinical trial, so it is not possible to determine a priori the national procedure that is to be followed. Other Member States apply both Directives simultaneously to different operations within the same clinical trial. Attempts to streamline the process through informal coordination between Member States' competent authorities have been unsuccessful. There are also variations between national requirements as to the content of the technical dossier.”

2. Latest initiatives have been insufficient to yield meaningful impact on approval timelines for ATMPs containing or consisting of GMOs

In 2017-2019, initiatives were launched to reduce national discrepancies across the EU and facilitate the process for authorising clinical trials with investigational medicinal products containing or consisting of GMOs

In October 2017, the European Commission and the European Medicines Agency, in collaboration with the Member States' authorities, launched a [joint action plan on ATMPs](#) to facilitate the development and authorisation of these products in the EU for the benefit of patients. In an acknowledgement to how GMO requirements represent a major hurdle to ATMP developers, the European Commission has initiated dialogue with national competent authorities to address the interplay between the GMO and the medicines legislation to reduce discrepancies across the EU with regard to the application of GMO legislation to ATMPs containing or consisting of GMOs. The initiative has successfully resulted in many actions to clarify and harmonise national requirements:

- A [Repository of national regulatory requirements](#)
- A [Questions & Answers document](#), related to the interplay between the EU legislation on medicinal products and GMOs.
- Harmonised application forms for clinical research and Good Practices for assessment of GMO aspects of clinical trials:
 - A [common application form](#) and [Good Practice document^a](#) for Human cells genetically modified by means of retro/lentiviral vectors
 - A [common application form](#) and [Good Practice document^b](#) for gene therapies that contain or consist of AAV vectors
 - A [common application form^c](#) for investigational medicinal products containing viral vectors

^a Both endorsed by Austria, Belgium, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Luxembourg, Malta, the Netherlands, Portugal, Romania, Spain, Sweden, and Norway (released in July 2018 and last updated in October 2019)

^b Both endorsed by Austria, Belgium, Croatia, Czechia, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Luxembourg, the Netherlands, Portugal, Romania, and Spain (released October 2019)

^c Endorsed by Austria, Belgium, Croatia, Czechia, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Luxembourg, the Netherlands, Romania, and Spain (released in October 2019)

These initiatives were welcome as they aid the better understanding of requirements by sponsors and contribute to streamlining common implementation across Member States.

Recent experience indicates that these initiatives have been insufficient

Despite these developments, recent experience indicates that these initiatives have been insufficient as administrative complexity and lengthy application timelines for investigational medicinal products containing GMOs are still causing significant delay to clinical trials.

A survey of ATMP developers in early 2020 to characterise recent experiences with GMO applications for gene therapies in the EU sought to examine whether the adoption of common application forms had led to significant improvements in the timing and process for GMO approval of clinical trials. The survey results, based on 66 GMO applications filed since August 2018, including 17 applications using the common application forms, show that, despite improvements due to the EC-EMA Action Plan, the GMO approval process for clinical trials remains a significant hurdle leading to delays in the initiation of clinical trials and selective choice of countries (“forum shopping”) by sponsors. Some of the survey findings include:

- There is still a large variability among Member States in the timing for approval (up to 12 months in some countries), decisions for classification (contained use versus deliberate release and different risk classifications within contained use) and data requirements (content and format), despite the use of the common application forms and the EC guidance.
- The review and approval of GMO applications are not faster when applying for a second and subsequent trial with the same product.
- The available data indicate that common application forms are of limited use since, in most cases, additional data are still requested by the national GMO competent authority, such as national application forms, in addition to the common application form.
- Many survey respondents also indicated that the preparation and submission of the GMO package and the implementation at the clinical sites remain very time-consuming and resource intensive.

A summary of the survey findings can be found in the annex to this document.

Delays in clinical trials result in delays of potentially life-saving treatments

By temporarily lifting some GMO requirements for COVID-19 treatments and vaccines, EU authorities have recognised that the EU GMO legislation is responsible for delays in clinical trials despite the recent initiatives. The exceptional circumstances of the pandemic highlight the urgency (“*time is of the essence*”) for finding a vaccine or treatment for COVID-19 and “*every month gained ... saves lives, livelihoods*”.

Time is also of the essence for people with cancer, inherited diseases, and other life-threatening conditions. Nearly every ATMP in clinical development addresses a life-threatening condition with an unmet medical need. Every month lost for treatment with an ATMP could reduce the survival chances or result in irreversible progression of the disease and loss of function. The measures taken to save lives during the pandemic can also save lives in normal (non-pandemic) circumstances.

3. Now is the time to re-evaluate GMO requirements for ATMPs

In view of the significant efforts made to streamline the GMO process for ATMPs, where, in effect, there has been only insufficient progress, it is time to evaluate the purpose and assess the impact of the GMO legislation and overhaul its application to gene therapies. The new EU Pharmaceutical Strategy provides a perfect opportunity to this effect.

After evaluating the effectiveness of previous non-legislative measures, as well as the potential of the latest temporary applicable measure set out in Regulation (EU) 2020/1043, we consider that an effective and future-proof solution can be best achieved by legislative means. A possible route is for the European Commission to consider the implementation of an exemption regime from complying with GMO requirements for ATMPs containing or consisting of GMOs undergoing clinical trials, considering that their environmental risk is often negligible.

Without effective harmonisation and significant simplification of the GMO registration process for clinical trials with ATMPs consisting of or containing GMOs, it will also be difficult for developers to leverage the advantages of the improved Clinical Trial Regulation. Ensuring a harmonised, science-based and consistent approach on GMO requirements for investigational ATMPs across all Member States is important to achieve the objective of the Clinical Trial Regulation and increase the EU's attractiveness as a leading region for clinical development. In addition, no change to the application of GMO requirements for ATMPs will constitute a direct impediment to achieving the EMA's Regulatory Strategy to 2025 for promoting innovation in the EU. Most importantly, since the majority of the ATMPs currently in development address serious unmet medical needs and are potentially life-saving, an expedient approval of clinical trials would reduce time for marketing authorisation and patient access, meaning more lives could be saved or significantly improved.

Therefore, we call on the European Commission to use its right of initiative to put forward a legislative proposal amending the existing legal framework, or, if deemed sufficiently effective, to adopt implementing legislation to supplement the current legal framework, with a view to accelerating clinical development, and ultimately patient access to life-changing and life-saving gene therapies.

The undersigned organisations are willing and prepared to engage with the European Commission and other stakeholders to jointly find the best solutions. Without action, the EU risks falling further behind the rest of the world in the development of novel treatments to the most challenging of medical conditions, and more importantly, in securing the access of patients to transformative, potentially life-saving therapies.

About the Alliance for Regenerative Medicine:

The Alliance for Regenerative Medicine (ARM) is the leading international advocacy organisation dedicated to realizing the promise of advanced therapy medicinal products (ATMPs). ARM promotes legislative, regulatory and reimbursement initiatives in Europe and internationally to advance this innovative and transformative sector, which includes cell therapies, gene therapies and tissue-based therapies. Early products to market have demonstrated profound, durable and potentially curative benefits that are already helping thousands of patients worldwide, many of whom have no other viable treatment options. Hundreds of additional product candidates contribute to a robust pipeline of potentially life-changing ATMPs. In its 11-year history, ARM has become the global voice of the sector, representing the interests of 370+ members worldwide and 70+ members across 15 European countries, including small and large companies, academic research institutions, major medical centres and patient groups. To learn more about ARM or to become a member, visit <http://www.alliancerm.org>.

About EFPIA:

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the pharmaceutical industry operating in Europe. EFPIA is the voice on the EU scene of 1,900 companies committed to researching, developing and bringing to patients new medicines that will improve health and the quality of life around the world. To learn more about EFPIA, visit: <https://www.efpia.eu/>

About EuropaBio:

EuropaBio, the European Association for Bioindustries, promotes an innovative and dynamic European biotechnology industry. EuropaBio and its members are committed to the socially responsible use of biotechnology to improve quality of life, to prevent, diagnose, treat and cure diseases, to improve the quality and quantity of food and feedstuffs and to move towards a bio-based and zero-waste economy. EuropaBio represents 75 corporate and associate members and 17 national biotechnology associations and bioregions. Read more about our work at www.europabio.org

References:

¹ ARM report “Clinical Trials in Europe: Recent Trends in ATMP Development”, based on an analysis of all new clinical trials with ATMPs initiated between January 2014 and June 2019. Available at <https://alliancerm.org/indication-data/clinical-trials-in-europe/>

² H. Bachtarzi & T. Farries (2019). The Genetically Modified Organism Medicinal Framework in Europe, United States, and Japan: Underlying Scientific Principles and Considerations Toward the Development of Gene Therapy and Genetically Modified Cell-Based Products. *Human Gene Therapy Clinical Development*, 30(3):114-128

³ U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research, March 2015. Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products. Guidance for Industry.

⁴ US Food & Drug Administration CFR - Code of Federal Regulations Title 21. Available at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=25.31>

⁵ Case C-528/16, Judgement of the Court (Grande Chambre) of 25 July 2018 (request for a preliminary ruling from the Conseil d’Etat – France) – Confédération paysanne and Others v Premier Ministre, Ministre de l’Agriculture, de l’Agroalimentaire et de la Forêt. Available at <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A62016CA0528>

⁶ Statement by the Group of Chief Scientific Advisors “A scientific perspective on the regulatory status of products derived from gene editing and the implications for the GMO directive”. 13 November 2018, available on https://ec.europa.eu/info/publications/status-products-derived-gene-editing-and-implications-gmo-directive_en

⁷ MP Hirakawa et al. Gene editing and CRISPR in the clinical: current and future perspectives. *Bioscience Reports* (2020) 40; <https://doi.org/10.1042/BSR20200127>

⁸ Regulation (EU) 2020/1043 of the European Parliament and of the Council of 15 July 2020 on the conduct of clinical trials with and supply of medicinal products for human use containing or consisting of genetically modified organisms intended to treat or prevent coronavirus disease (COVID-19)

Annex

Recent Experiences with GMO applications of Advanced Therapy Medicinal Products

Executive Summary

A survey was performed to characterise recent experience with the environmental risk assessment (ERA) by national competent authorities in Europe which is required to conduct clinical trials with Advanced Therapy Medicinal Products (ATMPs) containing or consisting of Genetically Modified Organisms (GMOs). The objective was to evaluate whether the guidance for common approaches and common application forms published by the European Commission and relevant national competent authorities were efficient to reduce the complexities and national differences resulting from the European GMO legislation for clinical trials with ATMPs.

Responses from ARM member organisations were collected between March and April 2020 and included information on a total of 66 GMO applications for products with no marketing authorisations and 7 GMO applications for products with a marketing authorisation.

Key findings indicate:

- There is important variability among EU Member States (MS):
 - The review of GMO applications by national competent authorities for clinical trials with ATMPs containing or consisting of GMO takes between 0 (no approval required) and up to 12 months to approve, depending on the country and type of ATMP.
 - GMO authorities of different MS use different legal basis for conducting the national assessment, i.e. either Directive 2001/18/EC on the deliberate release or Directive 2009/24/EC on the contained use of GMOs.
 - The risk classification attributed by individual MS to a product undergoing a multinational trial and even within a MS to a product undergoing multiple trials in that country can vary.
 - The data requirements for ERA submission differ, both in content and in format, from MS to MS for a same product. The use of Common Application Forms does not have a significant impact to harmonise the data required.
 - The possibility for clinical trial sponsors to interact with GMO authorities and address questions before or during the assessment of applications varies widely depending on the MS.
- GMO applications are responsible for delays in clinical trial initiation:
 - The approval by GMO authorities is granted after approval of the clinical trial by health authorities in approximately a third of the applications reported in the survey.
 - Complying with complex GMO requirements is time and resource intensive, both for clinical trial sponsors and for clinical trial sites.
 - The approval by GMO authorities is not faster for products which have already been subject to a former GMO ERA review and approval.
- The Common Application Forms were used in only 29% of the GMO applications reported in the survey. This limited use is partly explained by the timing of their endorsement and implementations in the different MS. However, in situations where these forms were used, additional information such as national application forms continued to be requested, limiting their usefulness for applicants.

- The use of Common Application Forms does not lead to a standardisation or streamlining of GMO applications.

It can therefore be concluded that based on the survey results, the GMO approval process for clinical trials with ATMPs containing or consisting of GMO remains a very complex and cumbersome process, leading to delays in the initiation of clinical trials, despite efforts in the last 2 years to streamline the process.