HGT

Regulatory Strategies for Accelerating the Translation of Gene Therapies to Clinical Practice: Focus on GMO Considerations

Joaquin Delgadillo,[1] Francisco Martin,[2–5,*] Gloria Carmona,[6] Josep M. Canals,[7–10] Paula Rio,[11,12] Cristina Eguizabal,[13,14] Felipe Prosper,[15,16] and Cristina Avendaño-Solá[17]

[1]Banc de Sang i Teixits (BST), Barcelona, Spain; [2]Department of Genomic Medicine, Pfizer-University of Granada-Andalusian Regional Government Centre for Genomics and Oncological Research (GENYO), Granada, Spain; [3]Department of Biochemistry and Molecular Biology III and Immunology, Faculty of Medicine, University of Granada, Granada, Spain; [4]Biosanitary Research Institute of Granada (IBS.GRANADA), University of Granada, Granada, Spain; [5]Excellence Research Unit "Modeling Nature" (MNat), University of Granada, Granada, Spain; [6]Red Andaluza de diseño y traslación de Terapias Avanzadas-RAdytTA, Fundación Pública Andaluza Progreso y Salud-FPS, Sevilla, España; [7]Laboratory of Stem Cells and Regenerative Medicine, Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain; [8]Creatio, Production and Validation Center of Advanced Therapies, University of Barcelona, Barcelona, Spain; [9]Institute of Neurosciences, University of Barcelona, Barcelona, Spain; [10]August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain; [11]Division of Hematopoietic Innovative Therapies, Centro de Investigaciones Energéticas Medioambientales y Tecnológicas and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIEMAT/CIBERER), Madrid, Spain; [12]Advanced Therapies Unit, Instituto de Investigación Sanitaria Fundación Jiménez Díaz (IIS-FJD, UAM), Madrid, Spain; [13]Advanced Therapies Unit, Osakidetza, Basque Centre for Blood Transfusion and Human Tissues, Galdakao, Spain; [14]Cell Therapy, Stem Cells and Tissues Group, Biobizkaia Health Research Institute, Barakaldo, Spain; [15]Servicio de Hematologíá y Terapia Celular, Clínica Universidad de Navarra (CUN), Cancer Centre Clínica Universidad de Navarra (CCUN), Pamplona, Spain; [16]CIBERONC, Madrid, Spain; and [17]Clinical Pharmacology Department, Hospital Universitario Puerta de Hierro-Majadahonda, IDIPHISA, Madrid, Spain.

Gene therapy has revolutionized modern medicine by offering innovative treatments for genetic disorders, cancers, and immune-related conditions through technologies such as viral vector delivery, genome editing, and genetically modified cell therapies. Despite significant advancements, the classification of gene therapy medicinal products (GTMPs) as genetically modified organisms (GMOs) under EU legislation imposes significant regulatory burdens, hindering early and timely patient access to such therapies. Current GMO regulations, originally designed for agricultural biotechnology, require environmental risk assessments (ERAs) and additional approvals, creating delays and increasing costs—with a particularly negative impact on early academic research. This article examines the scientific and regulatory discrepancies in classifying GTMPs as GMOs, arguing that replication-deficient vectors and non-persistent modified cells may not meet the criteria for GMOs. We highlight the negative impact of GMO requirements on clinical trial feasibility in Europe compared to the U.S., where a categorical exclusion from ERA applies to investigational medicinal products. Proposed solutions include adopting a risk-based regulatory model, harmonizing ERA processes under the revised EU Clinical Trials Regulation, and establishing exemptions for low-risk therapies. By aligning regulatory frameworks with scientific evidence, policymakers can accelerate the translation of gene therapies while maintaining safety standards, ultimately improving patient access to these transformative treatments.

Keywords: gene therapy, GMO regulation, environmental risk assessment (ERA), viral vectors, genetically modified cells, EU clinical trials, regulatory harmonization

INTRODUCTION

The field of gene therapy has emerged as a transformative area in modern health care, offering new therapeutic solutions for a wide range of genetic disorders, cancers, and immune-related conditions. Gene therapies involve various technologies, such as viral vector gene delivery, genome editing, genetically modified cell therapy, and virotherapy-based gene therapies.

One of the most notable advancements in this domain is the development of *ex vivo* gene therapies, based on genetically modified cells, such as chimeric antigen receptor (CAR) T cells (7 approved GTMPs) and genetically engineered hematopoietic stem/progenitor cells (HSPCs) (6 approved GTMPs). These therapies utilize gene therapy vectors to achieve the desired genetic modifications on target cells, optimizing their function and enabling targeted interventions for diseases that were previously untreatable.

In addition to *ex vivo* gene therapies, direct injection of adeno-associated virus (AAV)-based gene therapies has led to 8 approved treatments, including Luxturna® for

*Correspondence: Francisco Martin, Department of Genomic Medicine, Pfizer-University of Granada-Andalusian Regional Government Centre for Genomics and Oncological Research (GENYO), PTS, Av. de la Ilustración 114, 18016 Granada, Spain. E-mails: francisco.martin@genyo.es; martinmolinafrancisco@yahoo.es

DOI: 10.1177/10430342251372063

RPE65 mutation-associated retinal dystrophy, Zolgensma® for spinal muscular atrophy, and Hemgenix® for hemophilia B. These therapies use AAV vectors to deliver functional genes directly to affected tissues, offering long-term therapeutic benefits.

Similarly, virotherapy-based gene therapies have gained regulatory approval in oncology. Notable examples include T-VEC (Imlygic®), an oncolytic herpes simplex virus therapy for melanoma, or Oncorine, a genetically modified adenovirus approved in China for head and neck cancers. These virotherapies selectively infect and destroy cancer cells while stimulating an immune response, demonstrating their potential in cancer treatment.

A significant hurdle for gene therapy development involves compliance with regulations concerning genetically modified organisms (GMOs). In the European Union, GMO legislation was originally designed to protect food safety and the environment[1,2] but it also applies to medicinal products containing or consisting of GMOs. In addition, those directives have been transposed differently across EU Member States, resulting in regulatory fragmentation and interpretative discrepancies.[3]

Current EU regulation requires that any medicinal product consisting of or containing a GMO must undergo an environmental risk assessment (ERA) during its development. Consequently, to conduct a clinical trial with a product based on a GMO, the sponsor needs to obtain not only authorization from the Research Ethics committees and National Competent Authorities for medicines where the study is going to take place but also an additional authorization from different National Authorities to "release" or administer the GMO-containing medicinal product in that trial.[4] Moreover, since this EU legal framework was conceived for agricultural biotechnology, the data they require often lack relevance for medicinal product development.

This is burdensome for all those engaged in developing gene therapies, with a great impact on academic researchers who want to translate and facilitate the access of patients to the innovative approaches generated in the academic environment.

All authors of this are members of the Spanish Network of Advanced Therapies (www.redterav.es) and have contributed to this article exploring the regulatory challenges affecting the translation of *ex vivo* and *in vivo* gene therapies into clinical practice, with a focus on the challenges that come with their legal classification as GMOs, and the requirement to undergo systematic ERA and approval for release before they can be used in clinical trials. Furthermore, we propose future regulatory strategies for investigational medicinal products with a human therapeutic aim to reduce development burden and costs and facilitate early and broader patients' access to these transformative therapies.

SHOULD GENE THERAPY MEDICINAL PRODUCTS BE CONSIDERED GENETICALLY MODIFIED ORGANISMS?

Gene therapy medicinal products (GTMP) can be broadly categorized into three main types based on their mechanism of action and therapeutic approach: virotherapy, vectors, and genetically modified cells. Each of these plays a distinct role in achieving genetic modifications of patient cells, modifying biological functions for therapeutic purposes.

Virotherapy utilizes genetically modified viruses to treat cancer. These viruses are engineered to selectively infect and destroy tumor cells while minimizing harm to healthy tissues.

Vectors serve as delivery vehicles for therapeutic genetic material in all gene therapy strategies, ensuring that the desired gene or material reaches the target cells effectively. When delivered directly into the patients, the vectors are themselves the medicinal product. Viral vectors are derived from viruses by partially or completely removing the viral genes and replacing them with the therapeutic gene(s). In fact, most gene therapy vectors (AAV, LV, γRV, etc.) lack any viral gene in the final vectors, making them not only replication-deficient but also incapable of expressing any viral protein.

Genetically modified cells involve *ex vivo* genetic modification, where cells are extracted from a patient or donor, genetically engineered, and then reintroduced to provide therapeutic effects. Examples include genetically modified T cells or NK cells for cancer immunotherapy and genetically engineered HSPCs for the treatment of hematological and metabolic diseases.

As previously mentioned, although EU GMO regulations were primarily intended to protect food consumers and the environment, they also apply to medicinal products containing or consisting of GMOs according to the definitions set on EU Directive 2001/18/EC (on the deliberate release into the environment of GMO) and on EU Directive 2009/41/EC (on the contained use of genetically modified microorganisms).

EU Directive 2001/18/EC defines an "organism" as any biological entity capable of replication or of transferring genetic material and a "genetically modified organism" as an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.

EU Directive 2009/41/EC defines "micro-organism" as any microbiological entity, cellular or non-cellular, capable of replication or of transferring genetic material, including viruses, viroids, and animal and plant cells in culture, and "genetically modified microorganism" as a microorganism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.

Based on these definitions, virotherapy fulfills the definitions of GMO, as they involve intentional genetic modifications that alter viral properties, enabling them to replicate selectively within tumor cells, using competent viruses that can propagate within the body.

But one could argue whether other GTMPs fulfill the regulatory definitions of organisms and fall under GMO classification.

Viral vectors could be classified as non-GMOs because they lack the defining characteristics of an organism. Unlike replicating viruses, gene therapy vectors are replication-deficient, meaning they cannot propagate or survive independently in a natural environment. As GMOs are defined as self-sustaining biological entities capable of independent growth and reproduction, viral vectors do not meet this criterion. Instead, they function as delivery vehicles for therapeutic genes or genome editing tools, with no ability to replicate or alter ecosystems.

Genetically modified cells cannot survive or replicate independently in a natural environment. They do not possess self-sustaining biological functions, nor do they interact with ecosystems; they are designed to function within the individual's body without spreading beyond the intended therapeutic scope. Their survival time depends on the cell type and therapeutic purpose: CAR-T cells typically persist for weeks to months, with some showing long-term persistence in patients. Genetically modified HSPCs can survive for years, as they integrate into the bone marrow and continuously produce modified blood cells. But, importantly, none of these cells survive the life expectancy of the treated patients, in contrast with any GMOs, which are expected to be self-sustaining biological entities capable of independent growth, reproduction, and environmental interaction.

With regard to the new gene editing technologies, it is relevant to note that the Court of Justice of the EU decided in 2018 that the organisms obtained by new techniques of directed mutagenesis (i.e., gene editing) shall be classified as GMOs.[5] This decision was based solely on legal and procedural aspects, regardless of scientific or environmental considerations, and it differs from the decision taken in other regulated geographical areas.

In conclusion, we envisage the option of regulators establishing that certain technologies should not be considered as GMOs, based on scientific considerations and at least in the context of investigational medicinal products. However, this is likely to be a rather complex regulatory pathway and, unfortunately, with a limited impact, because this exception will probably not cover all gene therapies.

IMPACT OF GMO REQUIREMENTS ON GENE THERAPY CLINICAL DEVELOPMENT

Labeling gene therapies as GMOs introduces additional regulatory burdens that impact clinical development timelines, costs, and patient access within the European context.[6] In contrast, U.S. regulations accept a "categorical exclusion" from the requirements for ERA for gene therapy Investigational New Drugs.[7]

The additional regulatory requirements for investigational gene therapy-based medicinal products, linked to their classification as GMOs, include:

- ERAs: Developers must conduct studies on cell persistence, migration, and potential environmental impact, ensuring that modified cells do not spread beyond the intended site.
- Containment Measures: Facilities handling GMO medicinal products must comply with biosafety regulations, including specialized containment protocols to prevent unintended release.
- Public Consultation Requirements: Some EU countries mandate public consultations before granting GMO approvals, further delaying clinical trials and patient's access.
- Additional Documentation: Developers must submit detailed risk assessments addressing gene stability, potential horizontal gene transfer, and environmental exposure risks.
- For therapies using viral vectors, developers must conduct vector shedding studies to evaluate potential environmental risks.

These demands inflate the complexity, cost, and time needed to initiate clinical trials, rendering the EU a less favorable environment for early-phase gene therapy research relative to the U.S. The impact is especially negative if we bear in mind that early steps of research are often developed in academia, which might be more vulnerable to the risk that regulatory burden ultimately prevents the development of potential approaches and new therapies.

To overcome these hurdles, EU Member States and the European Commission launched in 2017 the Joint Action Plan on ATMP,[8] which included several initiatives for the harmonization and simplification of GMO documentation, such as good practice documents and common application forms concerning the conduct of clinical trials with human medicinal products consisting of or containing GMOs.[9–13]

They have also introduced, for certain categories of investigational medicinal products, a "specific ERA" on the basis that they are highly unlikely to pose a risk to the environment or to public health. Specific ERAs have been introduced as a mechanism to simplify and reduce the requirements for developers of certain categories of medicines containing GMOs.

Nevertheless, recent evidence shows that this has not led to significant progress in streamlining the regulatory burden imposed on GTMP clinical trials in the EU.[14]

ALTERNATIVE REGULATORY STRATEGIES

To address these issues, a revision of the regulatory framework governing gene therapy investigational products in Europe is imperative.

The current classification of certain GTMPs as GMOs entails additional scrutiny that is often disproportionate to the associated risk. A risk-based regulatory model should exempt products with well-characterized safety profiles—such as replication-incompetent vectors and non-persistent modified cells—from GMO-specific requirements[14,15] and rely solely on the assessments performed under medicinal products regulation.

The ongoing revision of the General Pharmaceutical Legislation[16,17] provides us with a precious opportunity to improve the EU regulatory framework in the right direction.

The current proposal aims to amend the EU Clinical Trials Regulation [Regulation (EU) 536/2014] and establish that to perform a clinical trial with investigational medicinal products for human use containing or consisting of GMOs, the sponsor will submit an ERA through the EU portal (CTIS) as part of the common application for the clinical trial. There will be, therefore, a single assessment of the environmental risk, performed at the Committee for Human Medicinal Products of the EMA (CHMP), that will be valid for all member states participating in the clinical trial. Both the European Parliament and the Council have already reached a consensus on the proposal and have endorsed this amendment to the clinical trials regulation.

While moving from multiple assessments to a single assessment is a positive step for multicenter trials, there is a risk that the final procedure will be equally cumbersome and disappointing for researchers. It is a fact that the EU CTIS implementation has caused an increase of bureaucracy and loss of flexibility for clinical trials in the EU, with a relevant impact on costs and delays.[18] There is a real risk that a centralized assessment via CTIS, with involvement of the already busy CHMP and consultations with member states, may even worsen the situation. The risk is especially relevant for early academic clinical trials to be conducted in a single site, where the application of centralized procedures at the EU level clearly adds complexity and burdens to the researchers.[19]

Therefore, the final regulation must allow a true risk-based approach, which will have to be established through the foreseen EMA Scientific Guidelines and the EU Commission delegated act. The new system should include: (1) exemptions from ERA submission for most clinical trials with investigational gene therapies, using a positive list of technologies where environmental risk is deemed to be known and/or negligible, and (2) Consensus on guidelines and Good Practice Documents that facilitate ERA in those cases of first-in-class products where an ERA should be submitted.

In the remaining period before the implementation of the new regulation, we should continue with the harmonization started with the common application forms and good practice documents,[9–13] and elaborate, as soon as possible, a positive list of technologies that might be exempted from regulatory revision of ERA. This list can be used by the Member States on a voluntary basis. Table 1 summarizes current requirements, its impact and the alternative proposals.

Scientists, developers, and regulators must work together to produce adequate guidance and ensure the right balance between the request to assess potential risks for the environment and establish mitigation measures and the necessity to

Table 1. *Environmental Risk Assessment in Clinical Trials with Investigational GTMP: Negative Impact of Current EU GMO Requirements and Alternative Proposals*

Current Requirements under EU GMO Legislation	*Impact*	*Proposed actions/solutions*
Submission for a GMO review for each clinical trial and each GTMP	Multiple submissions, increase burden and costs.	
ERA assessment case-by-case by each Member State's GMO authority.	Increase burden and costs for researchers and for public Administrations. Negative impact on scientific knowledge and open science principles	**Risk-based exemptions:** Exempt GTMP with minimal environmental risk
In multicentric trial, multiple applications and multiple ERA across different countries	Time delays, increase burden and costs for CT. EU seen as less favorable setting for GTMP CT as compared to other areas in the world	Preparation of a **positive list of technologies exempt from ERA review** before use in CT, due to a well-understood or negligible environmental risk
Different authorities for GMO assessment and for CT assessment	Regulatory uncertainty, delays, increased administrative burden	**Integration ERA /CT assessment:** ERA is a section of the IMP dossier for CT and a common ERA assessment is valid for all Member States
Containment Measures: Facilities must comply with country-specific GMO biosafety protocols	Time delays and increase costs	
Public Consultation Requirements	Delays to CT launch	**Specific ERA Frameworks:** Simplified assessments for specific known technologies, common ERA templates and guidances.
Specific ERA for each GTMP causes repeated experiments on persistence, migration, shedding	Waste of resources, negative impact on scientific knowledge	
Unclear GMO Classification for new GTMP.	Regulatory uncertainty, increased administrative burden and delays for CT with innovative GTMP. Particular impact on early studies, rare diseases and academic setting	**Revise GMO classification for investigational GTMP**, improving alignment with scientific knowledge and environmental risks

GTMP, gene therapy medicinal product; ERA, environmental risk assessment; GMO, genetically modified organism; CT, clinical trial.

ensure that new and effective gene therapies are developed for patients with unmet medical needs.

AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

FUNDING INFORMATION

The Spanish Network for Advanced therapies is supported by grants from the Instituto de Salud Carlos III, Ministerio de Ciencia, Innovación y Universidades, and European Regional Development Fund (ERDF): (RICORS TERAV (RD21/0017/0001) and RICORS TERAV+ (RD24/0014/0001). J.D. (RD21/0017/0022, RD24/0014/0037); F.M. (RD21/0017/0004, RD24/0014/0005); G.C. (RD21/0017/0015, RD24/0014/0030); J.M.C (RD21/0017/0020, RD24/0014/0016); P.R. (RD21/0017/0027, RD24/0014/0023); C.E. (RD21/0017/0024 y RD24/0014/0025); F.P. (RD21/0017/0009, RD24/0014/0010); C.A-S (RD21/0017/0028, RD24/0014/0021).

REFERENCES

1. Official Journal of the European Communities. (2001). Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the Deliberate Release into the Environment of Genetically Modified Organisms and Repealing Council Directive 90/220/EEC. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:L:2001:106:FULL&from=EN [Last accessed: June 30, 2025].

2. Official Journal of the European Union. (2009). Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the Contained Use of Genetically Modified Micro-organisms (Recast). Available from: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:125:0075:0097:EN:PDF [Last accessed: June 30, 2025].

3. Bachtarzi H, Farries T. 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. Hum Gene Ther Clin Dev 2019; 30(3):114–128; doi: 10.1089/humc.2019.042

4. European Commission. Genetically Modified Organism (GMO) Aspects for Investigational Medicinal Products. Available from: https://health.ec.europa.eu/medicinal-products/advanced-therapies/genetically-modified-organism-gmo-aspects-investigational-medicinal-products_en#latest-updates

5. Case C-528/16, Judgement of the Court (Grande Chambre) of 25 July 2018. Available from: https://eur-lex.europa.eu/legal-content/ES/TXT/PDF/?uri=CELEX:62016CJ0528 [Last accessed: June 30, 2025].

6. Iglesias-Lopez C, Obach M, Vallano A, et al. Hurdles of environmental risk assessment procedures for advanced therapy medicinal products: Comparison between the European Union and the United States. Crit Rev Toxicol 2019; 49(7):580–596.

7. US Food and Drug Administration. Code of Federal Regulations Title 21, Part 25. Environmental Impact Considerations. Subpart C—Categorical Exclusions. Sec. 25.31. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-25/subpart-C/section-25.31 [Last accessed: June 30, 2025].

8. European Commission DG Health and Food Safety and European Medicines Agency Action Plan on ATMPs. Available from: www.ema.europa.eu/en/documents/other/european-commission-dg-health-and-food-safety-and-european-medicines-agency-action-plan-advanced-therapy-medicinal-products-atmps_en.pdf [Last accessed: June 30, 2025].

9. Common application form for viral vectors contained in investigational medicinal products for human use. Available from: https://ec.europa.eu/health/sites/health/files/files/advtherapies/docs/vvs_caf_en.pdf

10. Common application form for investigational medicinal products for human use that contain or consist of AAV vectors. Available from: https://ec.europa.eu/health/sites/health/files/files/advtherapies/docs/aavs_caf_en.pdf [Last accessed: June 30, 2025].

11. Common Application form for clinical research with human cells genetically modified by means of retro/lentiviral vectors. Available from: https://ec.europa.eu/health/sites/health/files/files/advtherapies/docs/gmcells_caf_en.pdf [Last accessed: June 30, 2025].

12. Good Practice on the assessment of GMO related aspects in the context of clinical trials with AAV clinical vectors. Available from: https://ec.europa.eu/health/sites/health/files/files/advtherapies/docs/aavs_gp_en.pdf [Last accessed: June 30, 2025].

13. Good Practice on the assessment of GMO-related aspects in the context of clinical trials with human cells genetically modified by means of retro/lentiviral vectors. Available from: https://ec.europa.eu/health/sites/health/files/files/advtherapies/docs/gmcells_gp_en.pdf [Last accessed: June 30, 2025].

14. Beattie S, Hubert A, Morrell J, et al.; Alliance for Regenerative Medicine (ARM), European Federation of Pharmaceutical Industries and Associations (EFPIA), European Association for Bioindustries (EuropaBio). Call for more effective regulation of clinical trials with advanced therapy medicinal products consisting of or containing genetically modified organisms in the European Union. Hum Gene Ther 2021;32(19–20):997–1003; doi: 10.1089/hum.2021.058

15. Kenter MJH. Is it time to reform oversight of clinical gene therapy in the EU? Br J Clin Pharmacol 2019;85(1):8–10; doi: 10.1111/bcp.13795

16. European Commission. Proposal for a Regulation laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency. April 2023. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52023PC0193

17. European Commission. Proposal for a Directive on the Union code relating to medicinal products for human use. April 2023. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52023PC0192

18. EFPIA. Improving EU Clinical Trials: Proposals to Overcome Current Challenges and Strengthen the Ecosystem. 15 April, 2025. Available from: www.efpia.eu/media/pl0nag0s/efpias-list-of-proposals-clinical-trials-15-apr-2025.pdf [Last accessed: August 3, 2025].

19. Patrick-Brown TDJH, Bourner J, Kali S, et al. Experiences and challenges with the new European Clinical Trials Regulation. Trials 2024;25(1):3; doi: 10.1186/s13063-023-07869-x

Received for publication July 4, 2025;
accepted after revision August 5, 2025.

Published online: August 21, 2025.