ERGOMED

REGULATORY DASHBOARD

Genetically Modified Organisms (GMO) Regulatory Considerations for Advanced Therapies in Europe

ERGOMED Clinical Research

PRIMEVIGILANCE

GMO Legal Framework

In the European Union (EU), gene therapy medicinal products (GTMP) are a subset of advanced therapy medicinal products (ATMPs) and may consist of or contain genetically modified organisms (GMOs). GMOs are regulated by the European Commission (EC) Directive 2001/18/EC [1] primarily enacted for agricultural applications (GMO plants) to protect food consumers and the environment. Furthermore, EU legislation prescribes that GTMP-GMO clinical trials must comply with either Directive 2001/18/EC on the **deliberate release (DR)** into the environment of GMOs or/and with Directive 2009/41/EC [2] on the **contained use (CU)** of GMOs and EU member states' national environmental agency transpositions.

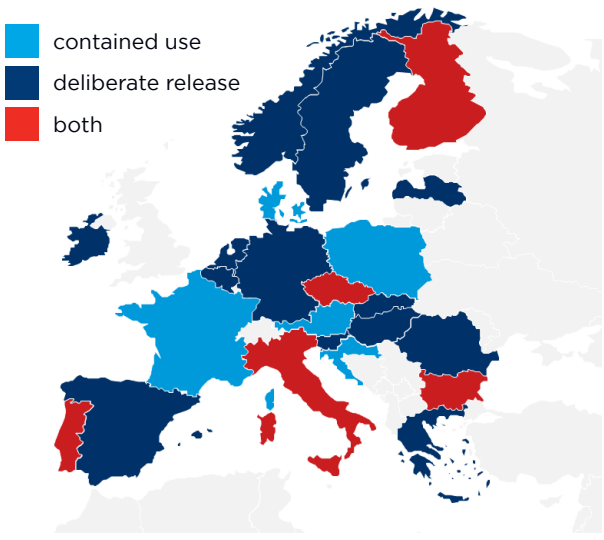


Figure taken from © 2021 State Institute for Drug Control [3]

Contained use: "the use of physical barriers, or the combined use of physical barriers, to limit contact between the GMO and the environment and to provide protection for the general public". *A rigid classification system (1-4), based on a proactive risk assessment, has enabled shorter review timelines.*

Deliberate release: "any intentional introduction into the environment of a GMO or a combination of GMOs for which no specific containment measures are used to limit their contact with, and to provide a high level of safety for the general population and the environment (virus shedding, and replication need to be considered)". *Regulatory procedures are more harmonized and stringent in terms of assessment timelines.*

The environmental risk assessments (ERA) for medicinal products containing, or consisting of, GMOs

The environmental risk assessments (ERA) for medicinal products containing, or consisting of, genetically modified organisms (GMOs) Scientific guideline[4] (2006) provides on the scientific principles and methodology to be used for the ERA[5] of a GTMP-GMO as laid down in Directive 2001/18/EC on the deliberate release of GMO into the environment. The ERA generally needs to consider potential adverse effects for persons (non-patients) directly exposed to the GMO, e.g., staff in the clinic involved in administering the product or in patient care; persons who may be in direct contact with the patient, e.g., family members and the 'general public'; and potential adverse effects for animals, plants, and micro-organisms, as well as the environment at large. The ERA does not concern any effects on the patient being treated, however effects on patients are important to consider while these might be indicative for possible effects on non-patients that are exposed to the medicinal product. If unacceptable risks are identified during the ERA, risk reducing measures are defined, and a conclusion on the acceptability of the remaining environmental risk is made.

Major GTMP-GMO enviromental risk considerations

A GTMP-GMO capable of **replication and dissemination or transmission** could possess an increased risk of being transmitted into the environment. Therefore, assays used to demonstrate that the GMO is not capable of replication (Replication Competent Virus, RCV) and dissemination, or transmission should have the same or better sensitivity as those used to detect the presence of the GMO in the environmental compartment. Considerations for vector infectivity, virulence, pathogenicity, and genetic sequence should be taken when developing a viral vector based GMTP[6]. Additional experiments may be included to further characterize the GMO found or suspected of **shedding**[6].

DEFINITION

Shedding
Shedding is defined as the dissemination of vectors through secretions and/or excreta and should be addressed in animal models and it is advised to integrate shedding studies into the design of biodistribution studies or other non-clinical studies, when feasible.

The aim of shedding studies is to determine the secretion/excretion profile of the virus/vector. Information collected from non-clinical shedding studies can then be used to estimate the likelihood and extent of shedding in humans and to guide the design of clinical shedding studies. These studies will pave the way to decide whether the risks resulting from its transmission into the environment are low or high. If the shedding pattern is known, there is no need for additional evaluations.

In contrast, in the US, as per Food and Drug Administration (FDA) 21 CFR 25 Environmental Impact and Consideration [7], GMO gene therapies are subjected only to general ERA requirements that are applicable to all drug products. A GMO risk assessment for advanced therapy is generally not required because clinical trials using a GMO will not significantly affect the environment as they are closely monitored and limited to a designated study group and since 2015 a "categorical exclusion" for investigational (GMO) advanced therapeutics and vaccines has been adopted. Rigorous local oversight is provided by Institutional Review Boards and Institutional Biosafety Committees (IBC). IBCs are the institutional bodies responsible for oversight of activities involving biohazardous materials as required by the NIH Guidelines. IBCs evaluate the sites' capability for safe storage, handling, administration, and disposal and shedding of gene-modified biohazardous materials.

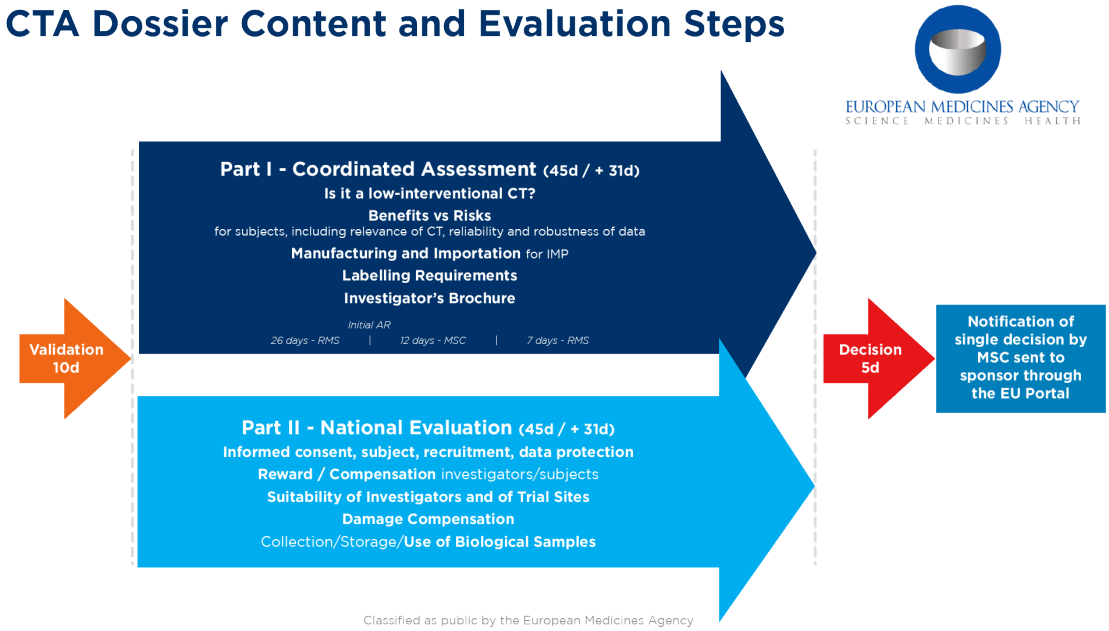
A complex EU GMO framework compared to the US Gene therapy product clinical development is slowed by the cumbersome GMO EU legislation. Furthermore, in vivo gene editing is considered a GMO according to the 2018 Court of Justice ruling that "organisms obtained by the new techniques of directed mutagenesis are considered GMOs and are, therefore, subject to the obligations laid down by the GMO directive. This makes the EU less attractive as a region to conduct clinical trials with investigational gene therapies causing detriment and delay to EU patients in need of GMO-based curative medicinal products.

Clinical Trials Regulation (CTR) EU No 536/2014 overview and GMO considerations

The review of GMO applications i.e., GMO Master Dossier, 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 GTMP-GMO. Typically assessment timelines for deliberate release tend to be long in Germany (up to 260 calendar days) and shorter in Spain, ca. 90-115 c. days, whilst assessment timelines for contained use are longer in the UK and France (up to 110 c. days) and shorter in Denmark and Italy (up to 45 c. days).

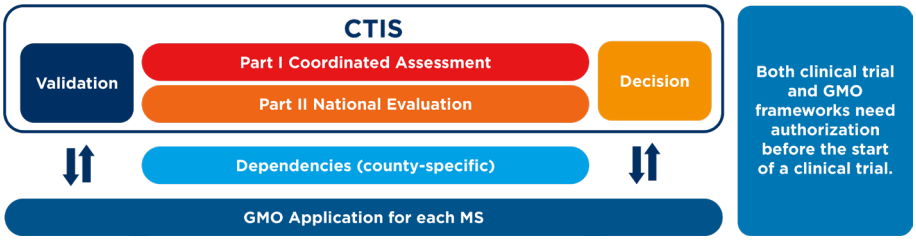
Since 31 January 2023, the Clinical Trials Regulation (CTR) EU No 536/2014 [8] has officially replaced the Clinical Trials Directive (CTD) 2001/20/EC [9], and all initial applications of interventional clinical trials for investigational medicinal products (IMPs) must be submitted under the CTR 536/2014, while ongoing CTD 2001/20 approved trials may continue until 30 January 2025 before transitioning to CTR 536/2014. According to Article 91, CTA 536/2014 is without prejudice to Directives 2001/18/EC and 2009/41/EC, meaning that these Directives still apply.

The CTR 536/2014 is intended to harmonise and centralise clinical trial application (CTA) requirements across EU member states (MS) by providing one single entry point via the EU Portal Clinical Trial Information System (CTIS [10]) and facilitating evaluation and supervision procedures for conducting multinational trials. The CTIS application dossier overview is summarized in the below figure taken from www.ema.europa.eu/ [11]. The dossier content consists of two parts, Part I for the core scientific information and Part II for country-specific documents and information (one submission package per country). Part I undergoes a coordinated assessment by the member state concerned (MSC) under a reporting member state (RMS), meaning one round of request for information (RFI). Part II is assessed at the country level by each MS.



The environmental aspects of IMPs consisting of or containing GMO are outside of scope of the CTR 536/2014 (Article 91). For IMP-GMO, a separate GMO application is still required. The situation is further complicated by the differences in the transposition of these EU directives into national law in the EU member states, resulting in significant variability among EU countries, which is challenging for a sponsor to navigate when executing an EU multi-regional clinical trials [12].

According to the previous CTD 2001/20/EC for some MS (Belgium, Norway, Poland, Czech Republic, Slovenia, Romania, and Bulgaria) the GMO application needed to take place before the CTA submission, but according to Article 5(3)(b) of the CTR EU 536/2014 authorisation under the GMO framework can no longer be a pre-requisite for a valid clinical trial authorisation application. Validation of a CTA application dossier is independent of GMO (framework) clearance or timing of ERA submission. However, some countries may still have interdependencies [13] e.g., site GMO approval to be included in Part II dossier in CTIS. The biosafety dossier cannot be submitted via CTIS and must therefore be submitted in parallel via Common European Submission Portal (CESP) to the relevant MSC authorities. Nevertheless, when the IMP contains or consists of a GMO, compliance with the requirements under both the clinical trial and the GMO frameworks is required before the clinical trial can start. This means that sponsors that have obtained the authorisation under the clinical trials framework cannot start the clinic al trial until compliance with the GMO framework. Furthermore, MS GMO application timelines differ from CTR legislation.



Examples of country specific dependencies	
Country	**Application process**
France	Process changed in 2022: submission through online portal to ANSM since 1 June 2022. Sponsor to submit a single declaration (CU, containment class I GMOs, no or negligible risk) or application (higher risk classes, or DR) for the CT
Germany	Single submission of CTA and GMO to PEI. GMO submission in parallel to CTA (separate submission via CESP, not accepted prior to CTA via CTIS). Timelines cannot be fully aligned with CTA review (coordination possible if Germany RMS).
Netherlands	Standard procedure (novel, innovative products) reduced to 120 days. Simplified processes for specific product categories, depending on the characteristics of the GMO: • 28 or 56 days for AAVs and human cells genetically modified with retroviral or lentiviral vectors. • Copy procedure is 28 days (exact copy application for a different clinical site). Option for site platform application for specific product types (e.g., AAVs or GM-cells) covering multiple trials, independent of sponsorship.
Poland	Sequential, GMO approval to be included in Part II of the CTA through CTIS portal (site suitability).
Sweden	GMO submission in parallel to CTA being submitted via CTIS (separate submission via email, reference to the EU trial number).

CU: contained use, DR: deliberate release, AVV: Adeno Associated Virus
Figure and table adapted from Ruehle et al [22]

EU action plan on ATMP-GMO to harmonize national GMO frameworks

Before marketing, all medicinal products, including GTMP-GMO, must obtain an authorisation issued by the European Commission upon advice of the European Medicines Agency (EMA). Access to the Community market for GTMP-GMO is subject to the centralised procedure laid down in Regulation 726/2004/EC [14], but ERAs [4,5,15] are also assessed by national GMO authorities. Since 2017 [16], EMA has launched an action plan on ATMP-GMO recognizing the need to initiate a dialogue with national competent authorities to reduce the discrepancies across the EU regarding the application of GMO rules (directives on deliberate release or contained use).

The plan is intended to address issues relevant to both clinical trials and marketing authorisation and help create coherent approaches for the assessment of these novel products without changing the basic legislation. These improvements are part of the strategic reflection "EMA Regulatory Science to 2025" [17]. The initiative has successfully resulted in many actions to clarify and harmonize national requirements:

- A repository of national requirements [13].
- Interplay between the EU legislation on medicinal products and GMOs, Frequently Asked Questions [18].
- Three common application forms (CAFs), without prejudice to consultation requirements that exist under Directive 2001/18/EC (deliberate release):
    1. Common application form for investigational medicinal products for human use that contain or consist of Adeno Associated Virus (AAV) vectors [19].
    2. Common Application form for clinical research with human cells genetically modified [20].
    3. Common application form for viral vectors contained in investigational medicinal products for human use [21].

Each CAF lists which jurisdictions have adopted it (e.g., CAF for genetically modified human cells is accepted for GMO submission in Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy*, Latvia, Lithuania, Luxembourg, the Netherlands, Portugal, Romania, Spain, Sweden, and Norway), but additional country specific requirements need to be considered. Furthermore, CAF must be accompanied by a SNIF (summary notification information format for notifications concerning the deliberate release into the environment GMOs other than higher plants in accordance to article 11 of Directive 2001/18/EC. SNIF must be submitted through the E-Submission Food Chain platform (ESFC).

Considerations and suggestions on a lack of EU centralized application system

The absence of provisions to optimize GMO applications [22] has been highlighted by many stakeholders including EMA, national competent authorities, sponsors, and associations. An example is the publication of the paper in Human Gene Therapy [24], calling for ATMPs to be exempted from GMO legislation jointly authored by major trade associations such as the Alliance for Regenerative Medicine (ARM), European Federation of Pharmaceutical Industries and Associations (EFPIA), and the European Association of Bioindustries (EuropaBio). Some regulatory leeway should be considered by GMTP-GMO applicants, e.g., some GMO competent authorities are open to consider the possibility of covering the GMO assessment of the various clinical trials corresponding to the different phases of the same clinical development in a single GMO application, or they are open to consider the possibility of applying a streamlined procedure in respect of multiple trials with the same product [18].

Furthermore, MSC as Germany, in response to the EU centralized CTIS, has uploaded in Paul-Enrlich-Institut webpage information on how to support CTA with GMOs [23]. Notwithstanding a lack in the EU of a complete harmonization and centralization for GMO applications, the EU has demonstrated flexibility in response to the COVID pandemic by releasing the Regulation (EU) 2020/1043 [25] and it is actively planning to facilitate the entry in the market of innovative medical products as GMTP-GMO.

* In Italy, these have been endorsed by the competent authorities responsible for the implementation of the Directive 2009/41/EC on the contained use of genetically modified micro-organisms only.

Conclusions

The EU GMO frameworks were developed to address environmental concerns related to GMOs for agricultural use. GMO frameworks are not centralized, and the inclusion of GTMP-GMO has created extreme variability when seeking clinical trial and marketing authorisation application (MAA) approvals due to national requirements not designed with medicinal products in mind.

Based on extensive experience at **ERGOMED**, key takeaways are:

- GMO framework harmonization is required to avoid prolonged development timelines and delays in the availability of advanced therapies for diseases with unmet medical needs.
- CTR 536/2014 has centralized the clinical trial framework, but it excludes the GMO framework. An independent GMO approval is required before the start of a clinical trial.
- Building a strategic GMO regulatory road map regardless of the development stage to help achieve objectives.
- Understanding and mitigating regulatory GMO challenges e.g., establishing GMO assessment pathways for clinical trials with an authorized GMO product covering an indication not foreseen in the Summary of Product Characteristic (SmPC), e.g., adult vs. paediatric population usage, or for clinical trials involving an authorised product in cases where changes have been made to the product composition (active substance). This can be helpful for emerging biotech companies, for extension of indications (EOI) or repurpose.

Selecting an experienced partner like **ERGOMED Clinical Research** to support sponsors' GMTP-GMO clinical development and navigate pitfalls as well as incessantly monitor the ever-changing* framework surrounding clinical trials on medicinal products containing or consisting of GMO.

* E.g. On July 13, 2023, The Swedish Medical Products Agency (MPA) and the Swedish Work Environment Authority (AV) which cooperate in the regulation of clinical trials of medicines that contain or consist of GMOs or GM microorganisms (GMMs) issued a guideline containing information on legislation, procedures and a description on which documents need to be submitted to the MPA and AV.

Selecting an experienced PV provider like **PrimeVigilance** will help you to develop a pharmacovigilance plan which will enable:

- active collection of data on rare potential risks;
- rapid detection, prioritisation and assessment of emerging safety information derived from spontaneous reporting systems, observational studies and other data sources;
- prompt evaluation of the impact of detected safety issues on the benefit-risk balance of GTMP-GMO, taking into account exposure and effectiveness data;
- active surveillance of vulnerable populations, such as pregnant women and older people.

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ABOUT ERGOMED

Founded in 1997, Ergomed is dedicated to the provision of global specialized services in the pharmaceutical and biotech industry. Today, Ergomed supports pharmaceutical companies with services spanning all phases of clinical trials, post-approval pharmacovigilance, and medical information. Recognized internationally in both rare disease and oncology drug development for its expertise, Ergomed offers a full range of quality clinical research and clinical trial management services along with an industry-leading suite of specialized pharmacovigilance solutions.

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