

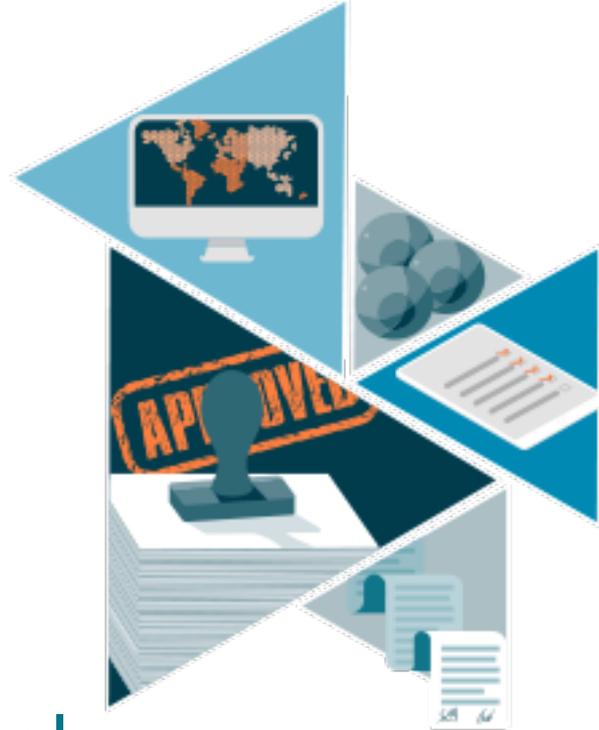
Regulatory Insights

REGULATORY PERSPECTIVE

Clinical trials with investigational medicinal products consisting of or containing genetically modified organisms: implementation of Clinical Trials Regulation EU 536/2014

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Although originally applicable to genetically modified crops, advanced therapy medicinal products (ATMPs), such as gene therapies, that consist of or contain genetically modified organisms (GMOs) and also viral-based vaccines, need to comply with the European Union (EU) GMO legislation, as implemented in each EU Member State before a clinical trial can commence. Under the European Clinical Trials Regulation 536/2014 (CTR) due to go live on 31st January 2022, a single electronic clinical trial application dossier will need to be submitted to all the Member States involved in the trial, via the European submission portal



(Clinical Trials Information System, CTIS). However, national documents, such as informed consent forms, will still need to be submitted, as part II of the dossier, to each *Concerned Member State*, also via CTIS. There will be a single coordinated and harmonized assessment of the clinical trial application between the involved Member States, with one country leading the coordination of the assessment (the *Reporting Member State*). The CTR has as yet not addressed GMO documentation (ERA, common application form, etc) required for an IMP with a genetic component. There is no defined interplay between the CTR and the current GMO legislative framework. There is no specified procedure, nor structure for submission of a GMO application via CTIS, as part of the new single submission and coordinated evaluation procedure for clinical trials defined by the CTR. Upcoming challenges to clinical trial sponsors under the CTR across Member States are identified in this article. Further, national GMO competent authorities are called upon to adopt a pragmatic and simple approach as a first step to facilitate the GMO assessment and its coordination with approval of a clinical trial application.

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INTRODUCTION

In recent years, across the European Union (EU) we have witnessed an increasing number of clinical trials with ATMPs and vaccines consisting of or containing genetically modified organisms (GMOs) [1]. As of 2021, approximately 15 ATMPs have received marketing authorization within the EU (with four subsequent withdrawals). Authorized COVID-19 vaccines in the EU include those that are genetically engineered and regulated as GMOs.

There are a variety of investigational medicinal products (IMPs) consisting of or containing GMOs (GMO-IMPs) [2]. Such GMO-IMPs include the following: human somatic cells modified *ex vivo* (for example, CAR-Ts); vaccines; recombinant virus-based vectors, including those containing genome editing nucleic acid sequences (which may also be delivered non-virally) and bacterial vectors.

Clinical Trials and GMOs are both regulated by European Commission (EC) directives across the EU, which allows for interpretation and implementation at national level. Due to the resulting complexity of the European Clinical Trials framework and the lack of harmonized requirements for GMO-IMPs across European Member States, the

initiation of clinical trials remains a time- and resource-intensive process. This can lead to delays to patient access to innovative and promising advanced therapy technologies. A pragmatic, simplified approach for the GMO assessment and its' coordination with the clinical trial authorization should be considered by each EU Member State.

In the EC communication about the Pharmaceutical Strategy for Europe (dated 25th November 2020) [3] the EC recognized that regulatory requirements for GMO products in the EU “*should be fit for purpose*” but are “*currently hindered by the fragmentation of national requirements*”.

The European Federation of Pharmaceutical Industries and Associations (EFPIA), the European Association for Bioindustries (EuropaBio) and the Alliance for Regenerative Medicine (ARM) have recently called upon the European Commission and the National Competent Authorities to exempt ATMPs containing or consisting of GMO, from the GMO legislation [4].

In July 2020, a temporary derogation from some provisions of the GMO requirements was granted for potential COVID-19 treatments and vaccines [5]. The exemption was made on the basis of a clear recognition of such complexities and resulting delays to

clinical development. This regulation was adopted with the intent to “accelerate the authorization and availability of successful vaccines against COVID-19”. The EU strategy for COVID-19 vaccines acknowledges that “There 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-center clinical trials in several Member States.” [6]. Further recited extracts from the regulation show how the EC recognized that the national requirements and procedures for the “environmental risk assessment and consent by the competent authority of a Member State is complex and can take a significant amount of time”. The Commission further acknowledged how their “Attempts to streamline the process through informal coordination between Member States’ competent authorities have been unsuccessful”.

The EC Pharmaceutical Strategy stated how “Solutions will be explored during the evaluation of the pharmaceutical legislation”. However, there is no timeframe towards such solutions, or ideally an exemption. The authors (EFPIA) hereby reiterate their support for a permanent exemption from GMO requirements for ATMPs containing or consisting of GMOs, as well as for vaccines.

The recent EC study on New Genomic techniques (NGTs) [7] was conducted to determine the need for regulating the use of new genetic tools differently to the currently applicable EU GMO framework. Reports, including the EC staff working document [8], were published recently and included important messages with regard to the burden of the GMO framework for ATMPs in Europe. The study states how “there are strong indications that” the GMO legislation is “not fit for purpose for some NGTs and their products, and that it needs adaptation to scientific and technological progress”. Per the feedback from trade associations, including that from EFPIA, the report acknowledges how stakeholders “consider that the GMO legislation is not specifically

designed for medicinal products and hinders the conduct of clinical trials.” The report also noted how stakeholders “ask for reconsideration of the application of the GMO legislation to medicinal products consisting of or containing GMOs. More specifically, they believe that there are no environmental and biosafety risks for non-replicating viral vectors or GM human cells, as these do not duplicate and cannot survive in the environment.” While the report does not specifically suggest that a legislative change to exempt ATMPs is the way forward, it does anticipate the need for policy instruments to “future-proof” legislation (as stated by the authors of the EC reports on NGTs).

The Clinical Trial Regulation (EU 536/2014) will be implemented and the Clinical Trial Information System will go live on the 31st of January 2022 [9–11] with a 3-year transition period. The Pharmaceutical Strategy proposes to find a solution to the fragmentation of GMO requirements amongst EU Member states, ideally through an exemption for ATMPs (and vaccines) by 2022. It is critical for the timely initiation of clinical trials with GMO-IMP that in the meantime, a pragmatic and simplified approach for the GMO assessment and its’ coordination with the clinical trial authorization should be considered at the national level by EU Member States, ideally with solutions towards greater harmonization of the GMO procedures.

CONTEXT & BACKGROUND

Current regulatory frameworks in Europe for clinical trials with investigational medicinal products with a GMO component:

1. Presently, two European legislations define the requirements to be followed prior to commencing a clinical trial with an IMP consisting of or containing a GMO across the EU:
 - ▶ The current **European Clinical Trials Directive 2001/20/EC**, as implemented in the different Member States, applies

to the evaluation of the clinical trial protocol, the information provided to the investigator (investigator brochure), the information provided to the participants (informed consent form), as well as the non-clinical, clinical, and quality module information about the IMP (IMP dossier, IMPD). The current European Clinical Trials Directive 2001/20/EC requires the submission of the IMPD to the national health competent authorities of the involved Member States by the sponsor. Additionally, a common module clinical trial application is submitted to the relevant ethics committees, by the investigators.

- ▶ The current European GMO Directives 2001/18/EC (Deliberate Release) and 2009/41/EC (Contained Use) are interpreted differently across different Member States and apply to the Environmental Risk Assessment (ERA) of the GMO component of the IMP and its use.

- ▶ EC Directive 2001/18/EC for Deliberate Release was enacted primarily to protect food consumers and the environment with regard to large scale agricultural use of GMO plants. Despite no negative environmental impact being reported after several decades culture of GMO crops, the subject remains controversial [12]. However, GMO medicinal products, such as gene therapies, are not designed to propagate in nature and cannot survive outside of controlled storage conditions. GMO medicinal products are utilized at several orders of magnitudes lower than GMO crops and after many decades of clinical development of GMO medicinal products, there have been no reports of any impact to the environment.

The application of the Deliberate Release or Contained Use Directives differ across Member States, sometimes even for the same GMO-IMP. When Deliberate Release has been identified by the authorities, this requires the submission of a dossier consisting of the GMO application, including the ERA and common application form (for an ATMP) by the sponsor to the corresponding national GMO competent authority of the Member State. In addition, information specific to the clinical trial site is in most cases also required. In case of an identified Contained Use, the procedure can also be complex and variable across the Member States.

2. Various data requirements and regulatory procedures exist in the different Member States for the ERA of the GMO component of the IMP:

The national GMO competent authorities differ (for nearly, but not, every Member State) from the national health authorities that evaluate the clinical trial evaluation application. In the majority of Member States, a single submission of both clinical trial and GMO applications is not possible, where the respective authorities do not necessarily interact with each other. Data requirements for a GMO application differ depending on whether it falls under either the Contained Use or Deliberate Release Directive and vary considerably in format and content across countries.

A first step to harmonization across Europe was taken in 2017 with the publication by the EC of a Common Application Form [13] to be used as part of the submission of the ERA dossier for Deliberate Release. Common application forms and good practice documents were introduced for a variety of ATMPs and vaccines, including for human cells genetically modified by retroviral or lentiviral vectors; and also, for adeno-associated viral vectors (AAV) and for other viral vectors. However,

additional forms and data are often requested by the national GMO competent authorities as recently shown by a survey (Clinical Trial implementation (CTi) Monitor 2020) [14] conducted by EFPIA and by the ARM 2020 GMO survey [4].

The European Commission hosts a website that provides overviews of the national regulatory requirements for GMO applications in the 27 EU Member States [15]. Since having been drafted in 2017, the overviews have not been kept up-to-date and many links to national websites no longer work.

In 2018, the European Commission published a Q&A document related to the interplay between the medicinal products framework and the GMO framework (regarding authorization procedures). The document acknowledged how “*The EU legislation governing the authorization of clinical trials does not specifically address environmental aspects.*” [16].

Despite these initiatives, the evaluation procedures (pathway and timelines) are very different across Member States. The EC acknowledged that there is not a common approach for assessment of GMO aspects of clinical trials with IMPs for human use in the EU when issuing the regulation specific to the temporary derogation from some provisions of the GMO requirements was granted for potential COVID-19 treatments and vaccines.

Four groups of Member States can be defined:

- ▶ Member States where a single application to the national health authorities including the GMO application takes place.
- ▶ Member States where separate GMO applications and clinical trial applications are conducted in parallel.
- ▶ Member States where the GMO approval is needed before the clinical trial application can be submitted.

- ▶ Member States where there is no defined process.

Those differences are illustrated for EU Member States that host the majority of clinical trials with GMO-IMPs in **Table 1**.

3. The European Clinical Trials Regulation 536/2014 (CTR) aims to harmonize the clinical trial application framework across Europe but does not address GMO applications (ERAs)

With the European Clinical Trials Regulation 536/2014 to become applicable on 31st January 2022 [10,11] a single electronic clinical trial application dossier will need to be submitted to all the Member States involved in the trial via a unique European portal (Clinical Trials Information System, CTIS). However, national documents, such as informed consent forms, will still need to be submitted, as part II of the dossier, to each *Concerned* Member State, also via the European platform (CTIS). There will be a single coordinated and harmonized assessment of the clinical trial application between the involved Member States, with one country leading the coordination of the assessment (the *Reporting* Member State).

The CTR has as yet not addressed the GMO documentation (ERA, common application form, etc) required for a GMO-IMP. There is no defined interplay between the CTR and the current GMO legislative framework. There is no specified procedure, nor, even a structure for a GMO application submission via CTIS, as part of the new single submission and coordinated evaluation procedure for clinical trials defined by the CTR.

If the national GMO procedures and their respective timelines (which vary across Europe) are not adapted to the CTIS and the CTR, the different GMO procedures and data requirements across Europe will continue to be required. It will be imperative to ensure GMO procedural timelines are synchronized with CTA timelines, in order to ensure

▶ TABLE 1
Regulatory GMO requirements in selected EU Member States.

EU member state	GMO competent authority	Submission	Contained use*/deliberate release**	Document and data requirements
Austria	BMSGPK (Federal Ministry of Social Affairs, Health, Nursing and Consumer Protection).	Parallel, or in advance of CTA	CU	Application in German, where technical documents in English accepted. GMO-IMPs not defined as somatic gene therapies (such as GMO vaccines) not required to submit request for authorization separate to the CTA.
Belgium	National Biosafety advisory Council (BAC) for DR. Service Biosafety and Biotechnology (SBB) and regional competent authorities for CU. Classification via Federal Agency of Medicines and Health products (FAMHP)/ National BAC.	Parallel, or in advance of CTA	CU or DR	Classification via FAMHP Scientific Technical Advice procedure. For DR 90-day assessment with 30-day public consultation required in local language (Dutch or French). For CU, typically shorter review time (30–70 days).
Bulgaria	Ministry of Environment and Water (MoEW).	Prior GMO authorization required	DR, where clinical sites should comply with CU requirements	Application in Bulgarian. Technical documents in English acceptable, except for information related to safety of clinical personnel. No public consultation. Plan for clinical site training and CV of PI required. Technical questions expected.
Finland	Board for Gene Technology.	Parallel, or in advance of CTA	CU or DR, depending on replicative capacity and containment measures	Applications in English may be acceptable in some cases. Public consultation when DR (60 days).
France	Ministry of Research (MESRI) for CU: GMO classification / CU agreement per clinical site. Ministry of Environment (MTES) for DR. High Council of Biotechnology (HCB) for opinion and assessment involved.	Parallel, or in advance of CTA	CU or DR (DR upon determination by HCB)	Class 1 is notification only. Via HCB for DR determination, If DR applies, an additional submission is required to MTES. Public consultation of 15-30 days may apply, in French. Electronic submission via DUO portal. In French#.
Germany	Paul-Ehrlich-Institut (PEI) with consultation of Federal Office of Consumer Protection and Food Safety (BVL), plus local GMO/Federal office of consumer protection and food safety.	Single submission via PEI in parallel, or separately in advance of CTA	DR	Single application includes CTA and GMO data. DR limits the GMO storage time to 6 months at site: any longer requires application for CU.
Ireland	Environmental Protection Agency.	Parallel to CTA	DR	28-day public notice. Agency decision 14 days after notice period#.
Italy	Ministry of Health (ISS) for CU Ministry of Environment for DR.	Parallel, or in advance of CTA	CU or DR	CU: form specific by class (1–4) Complex public consultation in case of DR (30 days), in Italian. Application in Italian#.

Table modified from Westra-de Vlieger *et al.* 2019 [17]. For recent industry timelines, please see Supplemental materials to 2021 *Human Gene Therapy* article [4].

*CU often required clinical site-specific notifications and/or submission to authorities.

**ERA requirements plus a dossier in the summary notification information format (SNIF) for publication on the EU register.

#Technical documents in English are acceptable.

TABLE 1
Regulatory GMO requirements in selected EU Member States.

EU member state	GMO competent authority	Submission	Contained use*/deliberate release**	Document and data requirements
Netherlands	Gene Therapy Office as single point of contact. Ministry of infrastructure, Environment and Water management (IenW) for permit application.	Parallel, or in advance of CTA	DR	Pre-submission meeting possible IenW require 120-day assessment for environmental risk for a GMO of unknown risk. For known risk, 56-day assessment. 28 days for “copy permits” across multiple clinical sites for a previously approved GMO.
Poland	Ministry of the Environment - GMO unit.	GMO authorisation required prior to CTA	CU	Public consultation required (30 days via GMO register); laymen summary of technical information required in dossier. Application forms in Polish [#] .
Spain	Consejo Interministerial de OMG (CIOMG) and Comisión Nacional de Bioseguridad (CNB).	Parallel, or in advance of CTA	DR	Questions focus on local site operations. GMO review and approval times may be extended if public consultation is sought. Application forms in Spanish [#] .
Sweden	Medical Products Agency (MPA).	Single submission, via MPA in parallel or separately in advance of CTA	DR	Single application to MPA for CTA and GMO aspects. SNIF and ERA required. Short, non-confidential, summary posted for public consultation via MPA website (30-day within 90-day assessment period).

Table modified from Westra-de Vlieger *et al.* 2019 [17]. For recent industry timelines, please see Supplemental materials to 2021 *Human Gene Therapy* article [4].

*CU often required clinical site-specific notifications and/or submission to authorities.

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[#]Technical documents in English are acceptable.

GMO assessment does not cause any undue delay.

TRANSITION PERIOD

As detailed in the European Commission draft Clinical Trials Regulation Q&A document (version 4 from July 2021) [18] upon the implementation of the Clinical Trials Regulation, there will be a 1-year transition period, during which sponsors will be able to selectively use the procedure that currently exists under the Clinical Trials Directive, submitting each clinical trial and GMO application to each national authority, without being required to use the CTIS portal. During the two subsequent years (leading to the end of January 2025 per the current timeline) it will be possible for ongoing trials

to remain under the Clinical Trials Directive framework, but all new clinical trial applications will have to be submitted under the harmonized framework of the CTR, via CTIS.

As a consequence, it will be difficult for a sponsor to leverage the advantage of the single dossier submission under the CTR, to initiate a clinical trial in Europe for an IMP with a GMO component. Moreover, the question of how these procedures would fit with the procedure and timeframe of the CTR is raised. That is, if the timings of both CTA and GMO assessments are not aligned, and a single simultaneous opinion cannot be provided, this can lead to a delay in the commencement of the clinical trial.

Implementation of a GMO exemption scheme before the end of the first year of the transition period for the CTR (the end

of January 2023) is important to avoid new CTA submissions for ATMPs under the CTR having to conduct the whole GMO assessment process in parallel. The same consideration also applies to vaccines.

IT IS IMPORTANT FOR EACH MEMBER STATE TO BE PREPARED FOR SUBMISSION OF NATIONAL GMO APPLICATIONS WHEN THE CTR IS IMPLEMENTED

It is important that each Member State prepares for the CTR implementation and to consider how the GMO application (that may include an ERA) will fit into the coordinated review of the clinical trial and its timelines.

Some countries have already adapted, or are in the process of adapting, their legislation to have a coordinated submission procedure to obtain an authorization under both GMO and clinical trial legislations in a timely manner, according to the latest intelligence, as reported for instance for Germany (see below for national case studies).

1. Understanding national readiness in view of CTR implementation

Each year since 2014, EFPIA has conducted a survey, the Clinical Trials Implementation (CTi) Monitor, to assess the national readiness for the implementation of the EU CTR. The latest survey was undertaken in November 2020 and was completed by the Pharmaceutical Industry National Trade Associations of 23 countries.

The executive summary, as published on the 6th of May 2021 [14] reads as follows:

“The European Clinical Trials framework will undergo a major change when the Clinical Trials Regulation 536/2014 [19] comes into application towards the end of January 2022. The legislation becomes a regulation, rather than a directive, which will ensure key aspects have identical rules throughout the EU.

EFPIA consider the implementation of the Clinical Trials Regulation to be an opportunity to demonstrate Europe’s commitment to clinical innovation, scientific collaboration, and transparency of clinical trials information.

In order to meet the essential elements for successful implementation of the Regulation and reaching its objectives, EFPIA has identified three key and distinct requirements as follows:

- ▶ *To deliver flexible, efficient, and streamlined execution of the authorization procedure to avoid administrative delays.*
- ▶ *To enable the required collaboration between concerned Member States, in addition to sponsors.*
- ▶ *To appropriately manage the transparency of data beyond the active phase of the clinical trial.*

In collaboration with EFPIA’s national trade association members, EFPIA are monitoring the preparation of the Regulation on the national level through our comprehensive National Trade Association Clinical Trials Implementation Monitor survey (CTi Monitor survey).”

In the 2020 edition of the CTi Monitor Survey, five specific questions were added to better understand the potential adaptation of the national legislation, as needed in context of GMO procedure requirements and the timeline for implementation of the CTR.

While the survey showed that four countries have already adapted their legislation with regard to the GMO procedure (17% of the 23 responding national trade associations) it also underlines that the majority of national trade associations had indicated that they “don’t know” if their country is planning to change its GMO legislation. In addition, no clear picture emerged from the response about the use of the Common Application forms for GMO applications. The use of the relevant common application forms would have indicated further harmonization of the

data requirements in the Member State. It is unclear whether these forms would be used and be part of the clinical trial application, or whether they would be submitted separately in addition to the clinical trial application; or, whether local GMO application forms would still be requested by some GMO competent authorities (often duplicating the content provided in the common application form).

As part of the 2020 CTi Monitor Survey, Pharmaceutical Industry National Trade Associations were asked the question: “Will the European Commission Common Application Forms for GMOs be part of the submission package (part II) for clinical trials under CTR?”. **Figure 1** illustrates the intended use of the relevant common application form, as part of the national GMO application as provided by the national trade associations.

Under the CTR, national health and GMO competent authorities need to be aware of the upcoming challenges related to the interplay between the clinical trial and the GMO legislative framework, with regard to procedures and data requirements for IMPs with a GMO component. Each Member State needs to ensure that a pragmatic and simple approach is in place to facilitate the GMO assessment and its coordination with the clinical trial authorization.

2. Member States' case studies (representative of similar challenges encountered across the European Member States)

Austria

Currently under the Clinical Trial Directive, where there are two separate, parallel processes.

Clinical trials with an IMP with a GMO component currently have to be submitted to both the Competent Authorities for medicines and the Ministry of Health preferably simultaneously. The Common Application Form for Clinical research shall be used. Plans are foreseen to evaluate potential adaptation

of the system towards a simplified process. For example, a combined approval of the clinical trial and GMO release authorization. As part of the GMO release authorization process the consultation (review) period could be reduced or, may no longer need to be performed. This outcome from the legislative process is still pending.

Belgium

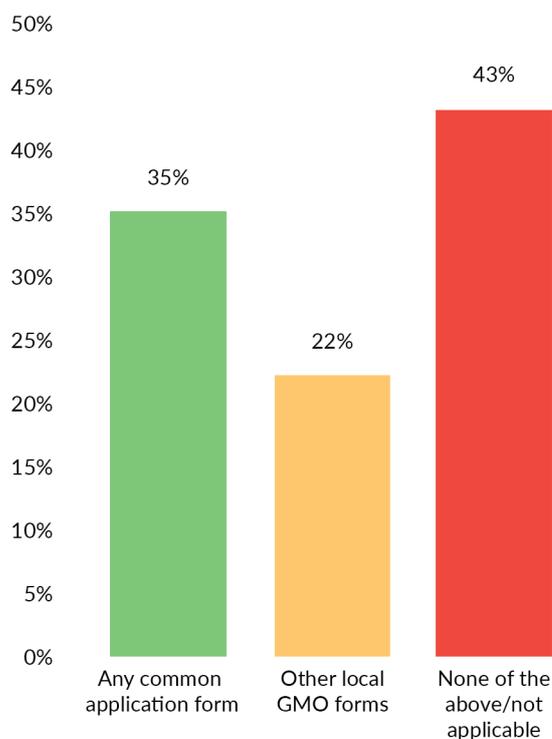
An adaptation of the current regulatory framework for clinical trials with GMOs should be foreseen to streamline and simplify the process under the CTR.

In Belgium, no adaptation of the existing legislation has been undertaken as yet, but the issue has been raised by the pharma industry trade association pharma.be.

Currently, under the Clinical Trial Directive, clinical trials with GMOs can fall under the Contained Use procedure and/or the Deliberate Release procedure.

► **FIGURE 1**

EFPIA CTi Monitor Survey: use of EU Common GMO Application Forms.



The Directive 2001/18/EC (transposed into Belgian law by the Royal Decree of 21st February 2005) applies to the Deliberate Release of GMOs and requires that an environmental risk assessment (ERA) should be carried out before release. The GMO dossier together with the clinical trial application is submitted to the national competent authority, the Federal Agency for Medicines and Health Products (FAMHP), which transfers the GMO dossier to the relevant advisory body, the Biosafety Advisory Council (BAC). This GMO dossier is then evaluated by the BAC, who thereby transmits their opinion to the FAHMP for a final decision.

The Contained Use procedure is implemented at regional level across Belgium (Brussels, Flanders, Wallonia). Each region has their own independent procedure, timeline and documentation in their regional language. A notification/authorization for the Contained Use (of the GMO-IMP) needs to be sent/obtained for each new study.

Most clinical trials under the Deliberate Release procedure will also necessitate the submission of a biosafety dossier according to the Contained Use procedure and the submission of a biosafety dossier according to the Deliberate Release procedure in addition to the submission of a CTA dossier to the ethics committee and the FAMHP (Figure 2) [20].

The EC common application forms are all currently implemented by the GMO competent authority in Belgium.

The procedure for the evaluation of these clinical trials with GMOs is complex and lengthy. Moreover, the environmental assessment embedded in the clinical trial evaluation procedure in case of a deliberated use of GMOs will, as such, not fit in the evaluation procedure foreseen under the CTR. For instance, it is unclear whether the documentation will be part of the CTA, as part I or part II, or how the different timeframes for the clinical trial and the GMO evaluation will be aligned.

Therefore, it is necessary to streamline and simplify this regulatory framework for clinical

trials with GMOs and to foresee its integration in the evaluation process according to the EU CTR and the Belgian *Law of 7 May 2017* implementing the CTR with adequate reduced timelines.

France

There is upcoming reform of GMO supervising authorities that include the Contained Use assessment of GMO medicinal products. Common Application Forms are currently implemented by the GMO competent authority in France.

The Haut Conseil des Biotechnologies (HCB) is the current independent authority in charge of reviewing applications for use of all types of GMOs (GMO plants and seeds, GMO animals and GMO medicinal products) that are submitted to public authorities by research institutions or sponsors. The HCB can also be consulted on ethical, economic and social aspects relating to GMOs.

Presently, under the Clinical Trial Directive, in case of a clinical trial application for a GMO-IMP in France, a submission for a Contained Use assessment is required in parallel of submissions to the French health authority (Agence Nationale de Sécurité du Médicament, ANSM) and the ethics committee. The Contained Use application for the GMO-IMP is sent to the Ministry of Research via an online portal by the clinical site(s). Either the EC common application form(s) or national forms are currently accepted for such applications. The Ministry of Research then refers to the HCB for GMO classification and for a permit for the clinical site(s). During its Contained Use assessment, the HCB mentions in its decision if there is a potential risk for the deliberate release of the GMO-IMP.

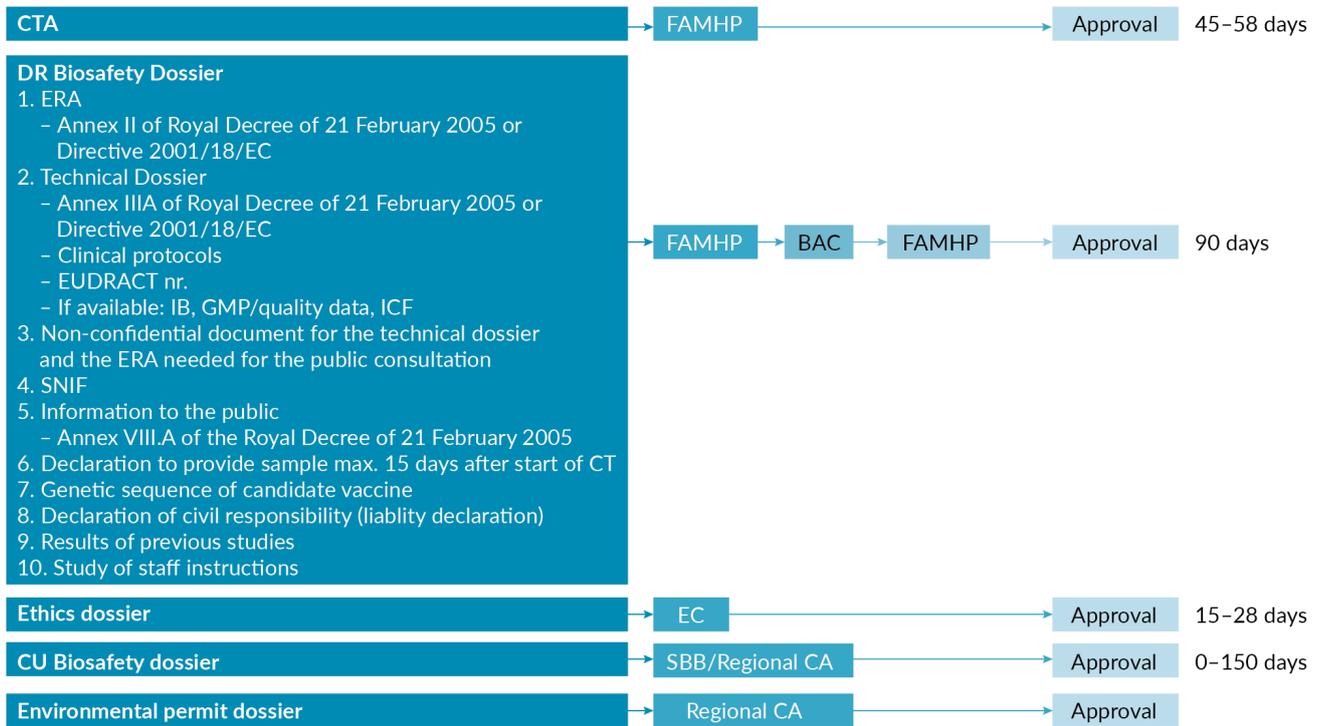
A reform of GMO supervising authorities including GMO-IMP Contained Use assessment is currently under discussion for implementation in early 2022.

Germany

A future joint process for the clinical trial and GMO under the CTR; with an additional

► **FIGURE 2**

Overview of the regulatory procedure in Belgium for a clinical trial with a GMO classified as deliberate release.



step to provide information specific to the GMO component.

The upcoming version of the German Drug Law (AMG) that will apply after implementation of the CTR, stipulates that the clinical trial authorization will also include GMO release authorization in the future. A release authorization, as determined by an assessment of the ERA, will also to be placed in the authorization via the CTIS to the sponsor in the future. Therefore, in Germany it is intended to be one process: the CTA via the CTIS, with authorization to include that for release of the GMO-IMP. An authorization from local federal state authorities will not be needed in the future.

The national trade association in Germany, the Verband Forschender Arzneimittelhersteller (VFA) underlines that there is a problem with the submission of the GMO data via the CTIS. The EC common application forms for GMOs will not be part of the submission package (neither Part I nor Part II) for the CTA, via the CTIS. For Germany, an

inclusion in Part II of the CTA dossier would result in regulatory problems, since the upcoming version of the AMG foresees that Part II is solely under the responsibility of the ethics committee. To resolve this CTIS issue, when a sponsor comes to apply for a clinical trial for a GMO-IMP, via the CTIS, the applicant will need to send a parallel application regarding the GMO aspects (based on the EC common application forms) via the Common European Submission Portal (CESP) to the GMO national competent authority. The deadlines are in parallel and the assessment by the national competent authorities will be undertaken jointly/in parallel. Objections and responses to GMO submissions must, again, be communicated separately, via the CESP, since these aspects are not included in the CTIS.

In Germany, there will be a clear procedure under the CTR to approve both CTA and GMO applications. An additional step will be needed to provide the information on the GMO aspects of the IMP. There could be

some challenges with regard to timelines for both assessments. When Germany is acting as the *Reporting* member state under the CTR, coordinating the procedure for the evaluation of the clinical trial, it can more easily control the timeline for the evaluation process, to alignment with their own national GMO procedures and requirements. When Germany is acting as a *Concerned* Member State, there will be the challenge to also include the full German GMO process within the overall EU assessment, since the timelines for the *Concerned* Member State are much shorter, in accordance with the CTR. It will be critical that the applicant ensures that the application is submitted in parallel (via the CTIS and GMO-related via the CESP) and that responses to GMO questions can be provided expeditiously.

It should be noted that the inclusion of the EC common application form(s) for GMOs in the CTIS was suggested by different stakeholders. During the consultations on CTR EU 536/2014, as well as during the “programming” of the CTIS, different EU Member States and national competent authorities, including the Paul-Ehrlich-Institute for Germany, had repeatedly proposed that the CESP should be opened to allow for submission of GMO applications to allow for the possibility of a synchronized approval of the CTA with authorized release of the GMO-IMP. These discussions are ongoing.

Spain

Currently under the Clinical Trial Directive, there are two separate and independent procedures: one for the CTA and another for evaluation of the GMO-IMP.

The Spanish law on GMOs (Law 9/2003 of 25th April, establishing the legal framework for the Contained Use, voluntary release and commercialization of GMOs and Royal Decree 178/2004, of 30 January, approving the General Regulations for the Development and Implementation of Law 9/2004, of 25 April, which establishes the legal basis for the Contained Use, voluntary release, and commercialization of GMOs) implements the EU

Directives on GMOs. No further adaptation is foreseen.

The GMO topic is addressed by a different competent authority (Ministerio para la Transición Ecológica y el Reto Demográfico) than the Spanish Pharmaceutical Authority (AEMPS) which assesses clinical trial applications, although AEMPS is represented in GMO assessment discussions. In Spain, since the CTA and GMO assessment procedures, including decision for approval, are separate and independent from each other, they can be performed in parallel, without issue in terms of timeline compatibility.

Common Application Forms are currently used by the GMO competent authority in Spain, as are the corresponding Good Practice documents on the assessment of GMO-related aspects in the context of clinical trials with for AAV clinical vectors and human cells genetically modified by means of viral vectors [21].

CONCLUSION

The initiation of a clinical trial with a GMO-containing IMP is currently a lengthy and complex process in Europe due to the fragmentation of the GMO requirements at the national level. Moreover, the different risk classifications and the different national procedures and requirements for the GMO assessment pose a challenge to align with the new coordinated evaluation of a CTA under the CTR. It will therefore be difficult for the sponsor of a clinical trial to leverage the advantage of the single dossier submission under the CTR to initiate a clinical trial in Europe in case of an IMP with a GMO component. Due to challenges described in this document and to the lack of clarity to sponsors, Europe appears less attractive to host clinical trials with GMO-containing IMPs than the United States, where ordinarily a “*categorical exclusion*” exists for gene therapies, vectored vaccines, and related recombinant viral or microbial products.

EFPIA, EuropaBio and ARM have recently called upon the European Commission and the national competent authorities to exempt

ATMPs and vaccines containing or consisting of GMOs from the GMO legislation [4]. EFPIA (and Vaccines Europe) reiterate their support to this *best-case scenario*, for both ATMPs and vaccines. An exemption from GMO requirements could make Europe a more attractive region for clinical development of, for instance, gene therapies and could accelerate European patients' access to these potentially life-saving medicines and vaccines.

In the meantime, concerns remain how all these different procedures for the GMO assessment will fit with new procedures and timeframes established under the CTR. There is a need to ensure that for each Member State a practical and efficient system is in place to allow for the GMO assessment of the IMP and its coordination with the clinical trial authorization at the time of the implementation of the CTR.

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With regard to this advocacy, the author is sitting astride joint trade association efforts (with frequent meetings) and welcomes input from the readers of CGTI to the issues highlighted in the article.

AUTHORSHIP & CONFLICT OF INTEREST

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