

MEDICINAL PRODUCTS FOR HUMAN USE CONTAINING OR CONSISTING OF GMOs: INTERPLAY BETWEEN THE EU LEGISLATION ON MEDICINAL PRODUCTS AND GMOs¹

FREQUENTLY ASKED QUESTIONS

VERSION 2

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¹ This document has not been adopted by the European Commission and, therefore, it does not contain the official position of the European Commission.

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Introduction

Medicinal products for human use may contain or consist of genetically modified organisms ("GMOs"²). In the EU, the marketing of such medicinal products is authorised by the European Commission and the environmental aspects thereof are addressed in the context of the marketing authorisation procedure.³

The authorisation of clinical trials with investigational medicinal products that contain or consist of GMOs falls under the competence of the Member States. The EU legislation governing the authorization of clinical trials⁴ does not specifically address environmental aspects. However, clinical trials with medicinal products that contain or consist of GMOs must comply with applicable requirements under the GMO framework. Specifically, the conduct of clinical trials can be regulated under Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms⁵ ("deliberate release framework") and/or under Directive 2009/41/EC on the contained use of genetically modified micro-organisms⁶ ("contained use framework").

For the purposes of this document, the term "GMO framework" is used to refer to the deliberate release framework and/or the contained use framework, as appropriate. An overview of national requirements (including information about the countries that apply the deliberate release framework and those that apply the contained use framework) can be found at https://ec.europa.eu/health/human-use/advanced-therapies/gmo_investigational_en.

This document addresses some frequently asked questions related to the interplay between the medicinal products framework and the GMO framework. The answers provided reflect the interpretation by the national competent authorities responsible for the application of the medicinal products framework and the GMO framework. In cases where a common interpretation does not exist across the EU, this is duly explained. It is therefore expected that this document will contribute to increase transparency and predictability for developers of medicinal products that contain or consists of GMOs.

² Throughout this document, the term "GMO" should be understood as covering both genetically modified organisms as defined under Article 2(2) of Directive 2001/18/EC, and genetically modified micro-organisms within the meaning of Article 2(b) of Directive 2009/41/EC.

³ See Article 6 of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L136, 30.4.2004, p.1).

⁴ Regulation (EU) No 536/2014 on clinical trials of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC, (OJ L158, 27.5.2014, p.1). Until the Regulation enters into force, Directive 2001/20/EC applies (Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, OJ L121,1.5.2001, p.34.)

⁵ 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 (OJ L 106, 17.4.2001, p. 1).

⁶ 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 (OJ L 125, 21.5.2009, p. 75).

It is stressed that the answers provided are only applicable to medicinal products for human use. Under no circumstances they can be extrapolated to medicinal products for veterinary use, or to GMOs that are not medicinal products.

The ultimate responsibility for the interpretation of EU legislation is vested on the European Court of Justice and therefore the content of this document is without prejudice to a different interpretation that may be issued by the European Court of Justice.

I. QUESTIONS RELATED TO AUTHORISATION PROCEDURES FOR THE CONDUCT OF CLINICAL TRIALS

1. Is the authorisation under the GMO framework a pre-requisite to the submission of a clinical trial authorisation application?

The conduct of clinical trials with investigational medicinal products that contain or consist of GMOs may require the prior authorisation of the competent authorities responsible for the clinical trials framework and for the GMO framework:

- Prior authorisation under the clinical trials framework is always required before a clinical trial can start in the EU.
- Prior authorisation under the Directive 2001/18/EC is mandatory in Member States that regulate the conduct of clinical trials under the deliberate release framework.
- Prior consent of the competent authorities under Directive 2009/41/EC may be required in Member States that regulate the conduct of clinical trials under the contained use framework, depending on the level of risk and whether the premises have already been authorised for activities involving the same level of risk.

The sequencing of the submissions of the relevant authorisation applications is not specifically addressed in the EU legislation. At present, no Member State considers the authorisation under the clinical trial framework as a prerequisite for the submission of applications under the GMO framework. However, in some Member States, sponsors are currently required to obtain authorisation under the GMO framework before the clinical trial authorisation application can be submitted.⁷ It is also noted that some Member States have implemented a single submission procedure, which permits the applicant to obtain authorisation under both GMO and clinical trials framework in a single decision.⁸

When the Regulation (EU) No 536/2014 on clinical trials becomes applicable, the prior authorisation under the GMO framework can no longer be a pre-requisite for a valid clinical trial authorisation application. Specifically, under Article 5(3)(b) of the Regulation, the assessment whether an application dossier is complete is to be done in accordance with the

⁷ The prior authorisation under the GMO framework is required in Bulgaria, Poland, Romania, Slovenia and Slovakia (situation in June 2018).

⁸ A single submission procedure has been put in place in Estonia, Germany, Greece, Lithuania and Sweden (situation in June 2018).

detailed provisions of Annex I. In turn, Annex I does not list the prior authorisation under the GMO framework as an element to be considered for the completeness check. Moreover, the assessment of the Member States concerned is limited to the aspects enumerated in Articles 6 and 7 of the Regulation and the lack of GMO authorisation cannot justify a negative decision by a concerned Member State.⁹

It follows that, when the Regulation (EU) No 536/2014 becomes applicable, an application for clinical trials authorisation cannot be turned down on grounds that the authorisation under GMO framework has not been obtained at the time when the application for clinical trial authorisation is submitted.

It is nevertheless recalled that, when the investigational medicinal product contains or consists of a GMO, compliance with the requirements under both the clinical trials framework and the GMO framework 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 clinical trial until such time as the legal requirements under the GMO framework have been complied with.

2. Is it possible to submit a single application to seek authorisation of GMO aspects for more than one clinical trial (corresponding to different phases of the same clinical development)?

Each clinical trial corresponding to a different phase of a clinical development requires separate authorisation under the clinical trial framework. Likewise, the authorisation of GMO aspects is also required in principle for each of the clinical trials.

However, 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.

It is acknowledged that, for most sponsors, it will be difficult to plan a full development program (uncertainty as to the performance of the investigational medicinal product, lack of resources to finance larger trials, *etc.*). However, sponsors that have a clear development program are invited to discuss with the GMO competent authorities the possibility of integrating the GMO assessment of subsequent phases of the clinical trial in the application for the earlier phase. A decision will be taken by the relevant competent authority on a case-by-case basis.

3. Is it necessary to apply for authorisation under the GMO framework for multiple trials with the same medicinal product?

Some GMO competent authorities are open to consider the possibility of applying a streamlined procedure in respect of multiple trials with the same product.

⁹ See Article 8 of the Regulation, in conjunction with Articles 6 and 7.

Sponsors that are concerned by this scenario are invited to discuss with the concerned GMO competent authority. A decision will be taken by the relevant competent authority on a case-by-case basis.

II. QUESTIONS RELATED TO THE SCOPE OF THE GMO FRAMEWORK

4. Is an authorisation under the GMO framework required in case of clinical trials with investigational products that have a marketing authorisation?

The GMO framework does not apply to medicinal products that have been granted a marketing authorisation.¹⁰ The exclusion of authorised medicinal products from the GMO framework is conditional upon the fact that a specific environmental risk assessment is conducted in the context of the marketing authorisation procedure. Any use of the medicinal product in accordance with the summary of product characteristics ("SmPC") is therefore exempted from the GMO framework.

However, the use of an authorised medicinal product in a clinical trial outside of the terms of the SmPC may involve environmental risks that have not been addressed during the marketing authorisation procedure and may therefore require assessment under the GMO framework.

In order to determine if the conduct of a clinical trial with an authorised medicinal product necessitates assessment under the GMO framework, the following scenarios may be distinguished:

4.1. *Trials with a medicinal product used in accordance with the SmPC.*

Clinical trials conducted with a medicinal product that is used in accordance with the SmPC do not require authorisation under the GMO framework as the GMO aspects of the conduct of the trial are fully covered by the marketing authorisation.

4.2. *Clinical trials with an authorised product but covering an indication not foreseen in the SmPC.*

The approach laid down in this section has been endorsed by Austria, Belgium, Cyprus, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Malta, Portugal, Romania, Slovenia, Spain, Sweden, UK and Norway.

Clinical trials with an authorised product which is used in a therapeutic indication not covered by the SmPC should be authorised under the GMO framework only with regard to new environmental risks not covered by the environmental risk assessment of the marketing authorisation. The following scenarios are given for illustration purposes:

- If the SmPC of an authorised gene therapy medicinal product foresees that the product should be used as a third line treatment and in the clinical trial the product is used as

¹⁰ See Article 12 of Directive 2001/18/EC and Article 3(3) of Directive 2009/41/EC.

second line treatment, the environmental risk assessment of the marketing authorisation can be deemed sufficient.

- If the SmPC of an authorised gene therapy medicinal product foresees that the product should be used in adult populations and the clinical trial is conducted with minors, the environmental risk assessment of the marketing authorisation can be deemed sufficient.
- If the SmPC of an authorised gene therapy medicinal product covers the treatment of melanoma but in the clinical trial the product is used for the treatment of leukaemia, assessment under the GMO framework would be required in respect of risks (if any) that are not covered by the environmental risk assessment of the marketing authorisation.

Sponsors wanting to conduct clinical trials with an authorised medicinal product but addressing a therapeutic indication not covered by the marketing authorisation are required to submit their intention to the GMO competent authorities (except in the case of Member States that have established a single submission procedure¹¹).

The submission under the GMO framework should focus on the new risks and not duplicate the assessment done in the context of the marketing authorisation procedure. In particular, the submission should provide (i) justification that the use of the product in the new indication does not carry any risk additional to those already covered by the ERA of the marketing authorisation, or (ii) description of the new risks. In case of new risks, risk minimisation measures and -where applicable- a SNIF should be provided.¹²

In cases where the sponsor considers that the environmental risk assessment of the marketing authorisation continues to cover all the risks (*i.e.* no new risks arising from the new indication), the competent authority will assess the information submitted by the applicant within a maximum period of 30 days. The competent authority will inform the applicant if it agrees (or not) with the sponsor's assessment that the environmental risk assessment of the marketing authorisation continues to cover all the risks of the product. If the competent authority agrees, a specific assessment of the conduct of the clinical trial under the GMO framework will not be required.¹³

If the competent authority does not respond within 30 days, it is understood that it agrees (tacit agreement) with the analysis of the sponsor that the environmental risk assessment of

¹¹ In the case of countries that have established a single-submission procedure (Estonia, Germany, Greece, Lithuania and Sweden) the notification should be done to the authorities of the single-entry point.

¹² A SNIF should be provided in the case of submissions made to the following jurisdictions: Belgium, Cyprus, Croatia, Czech Republic, France, Germany, Ireland, Italy, Romania, Slovenia, Spain, Sweden, or Norway.

¹³ In case of countries that have established a single-submission procedure, the deadline of 30 days does not apply. If additional information to assess GMO-related aspects is deemed necessary, this would be communicated to the applicant within the timelines of the clinical trial framework.

the marketing authorisation continues to address all the risks of the product and that a specific assessment of the conduct of the clinical trial under the GMO framework is not required.¹³

A submission form is provided in the Annex. It can be used in all jurisdictions that have endorsed the approach laid down in this section, except in the Czech Republic.

4.3. *Clinical trials with an authorised product but for a pharmaceutical form/route of administration not foreseen in the SmPC.*

The approach laid down in this section has been endorsed by Austria, Belgium, Cyprus, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Malta, Portugal, Romania, Slovenia, Spain, Sweden, UK, and Norway.

Clinical trials with new pharmaceutical forms and/or route of administrations should be assessed under the GMO framework only with regard to new environmental risks not covered by the environmental risk assessment of the marketing authorisation.

Sponsors wanting to conduct clinical trials with a new pharmaceutical form/route of administration for an authorised medicinal product are required to submit their intention to the GMO competent authorities (except in the case of Member States that have established a single submission procedure¹¹).

The submission under the GMO framework should focus on the new risks and not duplicate the assessment done in the context of the marketing authorisation procedure. In particular, the submission should provide (i) justification that the use of the product in the new pharmaceutical form and/or route of administration does not carry any risk additional to those already covered by the ERA of the marketing authorisation, or (ii) description of the new risks. In case of new risks, risk minimisation measures and -where applicable- a SNIF should be provided.¹²

In cases where the sponsor considers that the environmental risk assessment of the marketing authorisation continues to cover all the risks (*i.e.* no new risks arising from the new pharmaceutical form/route of administration), the competent authority will assess the information submitted by the applicant within a maximum period of 30 days. The competent authority will inform the applicant if it agrees (or not) with the sponsor's assessment that the environmental risk assessment of the marketing authorisation continues to cover all the risks of the product. If the competent authority agrees, a specific assessment of the conduct of the clinical trial under the GMO framework will not be required.¹³

If the competent authority does not respond within 30 days, it is understood that it agrees (tacit agreement) with the analysis of the sponsor that the environmental risk assessment of the marketing authorisation continues to address all the risks of the product and that a specific assessment of the conduct of the clinical trial under the GMO framework is not required.¹³

A submission form is provided in the Annex. It can be used in all jurisdictions that have endorsed the approach laid down in this section, except in the Czech Republic.

4.4. *Clinical trials with an authorised product in cases where changes have been made to the product composition (active substance).*¹⁴

Certain changes to the product composition can occur during the life-cycle of the medicinal product and they are handled via a variation procedure without the need for the generation of clinical trial data (*e.g.* changes in raw materials or excipients). These changes do not require assessment under the GMO framework.

However, there may be cases where clinical trials are conducted to confirm the safety or efficacy profile of an authorised product following a change in the composition thereof and in such cases assessment under GMO framework may be required. The following scenarios are given for illustration purposes:

- If a clinical trial is conducted to confirm the efficacy or safety profile of the authorised product following to a change in the vector, the conduct of the clinical trial should be assessed in full under the GMO framework.
- If a clinical trial is conducted to test a new encapsulation system of the active substance, a similar approach as described under 4.3 can be applied.

¹⁴ It is noted that certain changes to the composition of the product may require the submission of a separate marketing authorisation application as the new composition may be considered a different medicinal product. This issue is however not further elaborated as it is outside the scope of this document.

5. Are medicinal products that consist of plasmids subject to the GMO framework?

The interpretation provided in this section has been endorsed by Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Malta, Poland, Portugal, Romania, Slovakia, Spain, Sweden, UK and Norway.

It is noted that the interpretation provided for in this section has also been endorsed by the Committee for Advanced Therapies ("CAT"). Applications for marketing authorisation of ATMPs that consist of plasmids and which are submitted to the European Medicines Agency will therefore generally not be considered as containing or consisting of GMOs, as explained below.

Plasmids are not organisms and human beings are not regulated as GMOs.¹⁵ It follows that a medicinal product for human use that consists of one (or more) plasmid(s) does not fall under the scope of the GMO framework, even if it modifies the genome of the patient.

It is stressed that the above is only applicable if the medicinal product for human use does not contain other elements that warrant assessment under the GMO framework. For example, a plasmid that harbours a virus strain that has been genetically modified would be subject to the GMO framework.

6. Are medicinal products that contain or consist of genetically modified human cells subject to the GMO framework?

6.1. Human cells genetically modified with viral vectors

The interpretation provided in this section has been endorsed by Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, UK and Norway.

It is noted that the interpretation provided for in this section has also been endorsed by the CAT. Applications for marketing authorisation of ATMPs that consist of human cells genetically modified with viral vectors and which are submitted to the European Medicines Agency will be assessed by the CAT accordingly.

Human cells cannot proliferate in the environment as they can only survive inside the human body or under *in vitro* culture conditions. However, viruses that are used to modify the human cells are organisms that could proliferate in the environment. Therefore, investigational human cells genetically modified with viral vectors are to be regulated under the GMO legal framework focusing the assessment thereof on the viral vector.

¹⁵ See Article 2 (2) of Directive 2001/18/EC.

ATMP developers are invited to consult the 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.

6.2. Human cells genetically modified with plasmids

The interpretation provided in this section has been endorsed by Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Greece, Hungary, Ireland, Luxembourg, Malta, Poland, Portugal, Romania, Spain, Sweden, and UK.

It is noted that the interpretation provided for in this section has also been endorsed by the CAT. Applications for marketing authorisation of ATMPs that consist of human cells genetically modified with plasmids that are not integrative and non-replicative and which are submitted to the European Medicines Agency will therefore not be considered as containing or consisting of GMOs, unless the plasmid contains the genome of a full viral sequence.

Investigational medicinal products that consist of human cells that have been genetically modified with plasmids that are not integrative and non-replicative are not considered GMOs, provided that the plasmid does not contain a full viral sequence.

Annex

SUBMISSION FORM FOR USE IN CASE OF CLINICAL TRIALS WITH AUTHORISED MEDICINAL PRODUCTS

This application form can be used for submissions in the following jurisdictions: Austria, Belgium, Cyprus, Croatia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Malta, Portugal, Romania, Slovenia, Spain, Sweden, UK, and Norway.

SECTION 1 – ADMINISTRATIVE INFORMATION

1.1. Identification of the applicant

Organisation Name:	
Address Details:	
Contact person:	
Telephone No:	
Email Address:	

1.2. Identification of the sponsor (to the extent that is different from the applicant)

Organisation Name:	
Address Details:	
Contact person:	
Telephone No:	
Email Address:	

1.3. Information about the clinical trial¹⁶

a) General information about the clinical trial

EudraCT-number (where available):	
Objective of the study:	
Intended start and end date:	
Number of trial subjects that will take part in the study:	
Indicate if an application related to the same investigational medicinal product has been submitted -or is planned to be submitted- to other EEA Member States. In the affirmative, please identify the countries concerned:	

b) Intended location(s) of the study:

The applicant should provide information about the sites located in the country of submission of the application. In addition to the location of the clinical activities,¹⁷ the location(s) of laboratories¹⁸ in which activities with the GMO are carried out under the terms of this application should be stated (e.g. location of storage of the investigational medicinal product, location of storage of samples from clinical trial subjects that contain GMOs).

Organisation Name:	
Address Details:	
Contact person:	
Telephone No:	
Email Address:	

¹⁶ For applications submitted in Sweden -where a single submission procedure has been put in place- only the Eudra CT-number is mandatory.

¹⁷ The location of the site(s) where donation, procurement and testing of the donor cells take place need not be listed.

¹⁸ Laboratories that perform routine laboratory diagnostics analysis need not be listed.

Planned activities:	
Containment level:	
Name and contact details of the responsible person:¹⁹	

Organisation Name:	
Address Details:	
Contact person:	
Telephone No:	
Email Address:	
Planned activities:	
Containment level:	
Name and contact details of the responsible person	

(Applicant should complete as many tables as necessary)

¹⁹ The responsible person is either the person responsible for supervision and safety as provided for under Annex V of Directive 2009/41/EC, or the responsible scientist as provided for under Annex IIIA of Directive 2001/18/EC.

SECTION 2 –INFORMATION ABOUT THE INVESTIGATIONAL MEDICINAL PRODUCT

2.1 Characterisation of the finished investigational medicinal product

a) General information

Description of the finished medicinal product	Cell-based products:	Autologous <input type="checkbox"/> Allogeneic <input type="checkbox"/> Xenogeneic <input type="checkbox"/> If xenogeneic, specify species of origin: Specify type of cells (e.g. hematopoietic stem cells...):
	Gene therapy:	In vivo gene therapy <input type="checkbox"/> Ex vivo gene therapy ²⁰ <input type="checkbox"/>
		Viral vector used: Retrovirus <input type="checkbox"/> Lentivirus <input type="checkbox"/> AAV <input type="checkbox"/> Others. Please explain:
		Are the vectors used replication competent: Yes <input type="checkbox"/> No <input type="checkbox"/>
Bacterial-based product:	Please describe species and strain:	
Pharmaceutical form:		
Mode of administration:		

²⁰ For genetically-modified cells, the section on cell-based products should also be completed.

b) Information about the marketing authorisation

Date of authorisation by the European Commission	
Marketing authorisation number	
SmPC <i>The applicant should provide the most updated version of the SmPC.</i>	

SECTION 3 – INFORMATION ABOUT RISKS

The applicant considers that the conduct of the clinical trial which is the object of this submission entails risks not covered by the environmental risk assessment of the marketing authorisation:

Yes If ticked, please go to Section 3.1.

No If ticked, please go to Section 3.2.

3.1. New risks identified.

The applicant should provide a description of the new risks identified. In case of new risks, risk minimisation measures. In addition, if the submission is intended for Belgium, Cyprus, Croatia, France, Germany, Ireland, Italy, Romania, Slovenia, Spain, Sweden, or Norway, a SNIF should also be provided.

Identified risk(s)	Risk minimisation measure(s)

3.2. New risks not identified.

The applicant should provide a justification as to why it considers that the conduct of the clinical trial does not entail risks other than those already assessed in the context of the marketing authorisation procedure.

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