



Standard operating procedure

Title: Consultation of environmental competent authorities on genetically modified organisms with respect to environmental risk assessment for medicinal products for human use		
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1. Purpose

To describe the procedure to be followed for the consultation of environmental competent authorities in accordance with Article 6(3) of Regulation 726/2004.

2. Scope

This SOP applies to the Human Medicines Evaluation Division (E-Division and D-Division).

It relates to medicinal products for human use containing or consisting of GMOs. The responsible EMA committee assesses whether the product that is the object of a marketing authorisation application contains or consists of GMOs. During the pre-submission phase, the responsible EMA committee, supported by the EMA, confirms the GMO status and decides on whether consultation of the GMO authorities is applicable.

In case of variations/extensions to a marketing authorisation for a medicinal product for human use that contains or consist of GMOs, the responsible EMA committee takes the decision whether the variation/extension involves new risks for the environment that have not been considered as part of the assessment of the initial MAA. The consultation of the GMO authorities should only be triggered if the responsible EMA committee considers that the variation/extension involves new risks for the environment.

The responsible EMA committee should take due consideration of the Frequently Asked Questions on the interplay between the EU legislation on medicinal products and GMOs¹.

¹ https://ec.europa.eu/health/sites/health/files/files/advtherapies/2018_gmcells_qa_en.pdf



3. Responsibilities

It is the responsibility of the respective Head of Department and Office Heads to ensure that this procedure is adhered to. The responsibility for the execution of a particular part of this procedure is identified in the right-hand column of section 9.

4. Changes since last revision

Consultation process streamlined in agreement with the Committee for Advanced Therapies, Biologics Working Party and Committee for Medicinal Products for Human Use.

5. Documents required for this SOP

All documents and templates required for this SOP are located at X:\Templates\Others\H - Consultation of CAs on GMOs.

- List of GMO CAs
- Form 1: start of procedure Eudralink message
- Form 2: Evaluation timetable
- Form 3: Confidentiality agreement
- Form 4: consultation form – Specific ERA
- Form 5: consultation form – Non-Specific ERA
- Form 6: Overview of comments
- Form 7: EPAR email

6. Related documents

- SOP/H/3004: Tasks of the product team on the handling of the initial marketing authorisation application
- SOP/PDM/1004: Core master files of medicinal products for human and veterinary use following the centralised procedure
- EMEA/CHMP/BWP/473191/2006: EMEA Guideline on Environmental Risk Assessments for medicinal products consisting of, or containing, genetically modified organisms (GMOs) (<https://www.ema.europa.eu/en/environmental-risk-assessments-medicinal-products-containing-consisting-genetically-modified>)
- Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-scientific-requirements-environmental-risk-assessment-gene-therapy-medicinal-products_en.pdf
- Draft guideline *on quality, non-clinical and clinical aspects of 4 medicinal products containing genetically modified cells* (https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-quality-non-clinical-clinical-aspects-medicinal-products-containing-genetically_en.pdf)

7. Definitions

AR: Assessment report

CA: Competent authority, i.e. environmental competent authority established under Directive 2001/18/EC on genetically modified organisms

CAT: Committee for Advanced Therapies

CHMP: Committee for Medicinal Products for Human Use

Consulted CA: Consulted competent authority, i.e. those CAs that have undertaken an overall confidentiality agreement with the EMA as listed in "List of GMO CAs" or that have requested to be consulted and signed an ad hoc confidentiality agreement with the EMA

DREAM: Document records electronic archive management system

ERA: Environmental risk assessment

LoQ: Day 120 list of questions

LoOI: Day 180 list of outstanding issues

PL: Product lead supported by the product assistant as appropriate

Rapporteur: Rapporteur from the EMA responsible committee (CHMP or CAT)

8. General principles

The environmental aspects of medicinal products for human use containing or consisting of genetically modified organisms ("GMOs") are evaluated by the responsible EMA committee as part of the assessment of the marketing authorisation application ("MAA").² The GMO framework³ is not applicable to such MAAs.⁴

The assessment of environmental aspects of MAAs, which is performed by the responsible EMA committee, must respect the safety requirements laid down by Directive 2001/18/EC. To this effect, the MAA must contain (among others) the technical dossier with the information required under Annex III and IV of Directive 2001/18/EC and an ERA in accordance with Annex II of Directive 2001/18/EC. In addition, the Rapporteur shall carry out necessary consultations of GMO bodies.

The steps taken by Member States to adapt the provisions of the GMO framework to the specific characteristics of medicinal products for human use, including the adaptation of the technical information contained in Annex III of Directive 2001/18/EC and the development of specific ERAs for certain type of medicinal products should also be taken into consideration in the assessment of environmental aspects of marketing authorisations for medicinal products for human use that contain or consist of GMOs.

² The responsible EMA committee is the CAT in the case of ATMPs, the CHMP being the responsible committee for non-ATMPs.

³ 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) and 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).

⁴ Article 12 of Directive 2001/18/EC and Article 3.3 of Directive 2009/41/EC.

The consultation is under the responsibility of the Rapporteur. EMA coordinates the consultation under the Rapporteur's responsibility and oversight. Only the Rapporteur assesses the ERA. The Co-Rapporteur does not produce an ERA assessment.

The Rapporteur team may – as a matter of internal organisation of work - outsource this task (e.g. to a national GMO authority). In such cases, the consultation procedure must still be conducted in accordance with the medicines' framework (e.g. deadlines and consultation procedures under GMO framework are not applicable).⁵ The Rapporteur remains responsible for the questions that will become part of the list of questions in the ERA Rapporteur AR.

As a general principle, the consultation with the environmental authorities consists of a single-round, which takes place during the 1st phase of the MAA evaluation. However, the CAT (for ATMPs) and the CHMP (for non-ATMPs) may decide - on a case by case basis - to launch a second consultation where additional input from the environmental authorities is deemed necessary to address an identified risk.

The consultation starts at Day 80 with GMO CA comments expected by Day 110 at the latest.

- Day 1: EMA informs the GMO CAs of the procedure start and provides the consultation timetable for planning purposes.
- Day 80: EMA sends the ERA Rapporteur AR, Module 1.6.2 and a consultation form to GMO CAs for which EMA has a confidentiality agreement on records.

There are 2 types of consultation forms:

- Consultation Form for medicinal products that contain or consist of GMOs in respect of which a specific ERA.
- Consultation Form for medicinal products that contains or consists of GMO in respect of which there is no specific ERA.
- Day 110 at the latest: GMO CAs comments are received
- Day 120 LoQ: Rapporteur and the EMA responsible committee take due account of the comments from the environmental authorities. However, the content of milestone documents (including LoQ, assessment report, SmPC, PIL, RMP and ERA) is solely decided by the EMA responsible committee.

During the 2nd phase of the evaluation, the EMA responsible committee can decide, on a case by case basis, to request additional input from the environmental authorities to address an identified risk as follows:

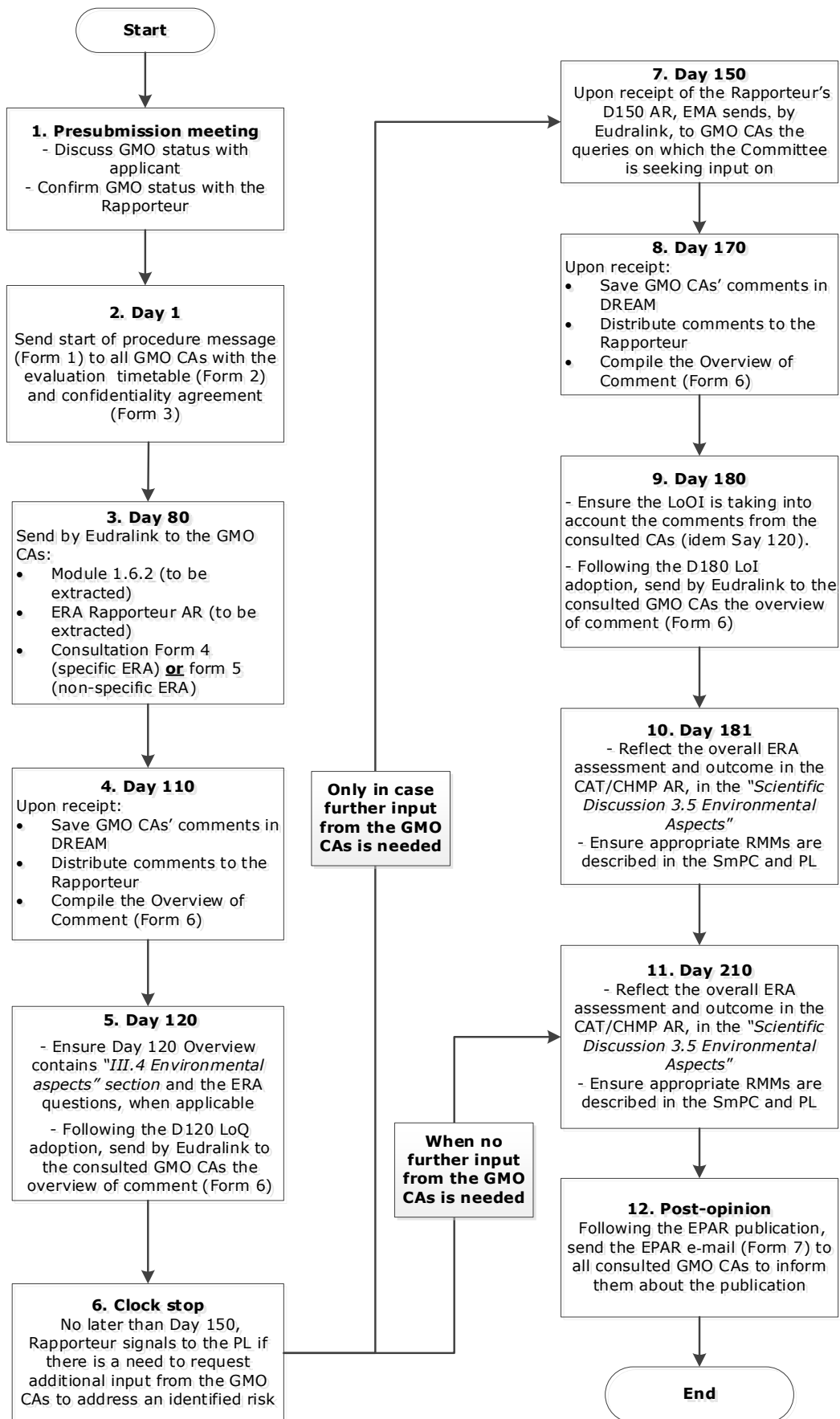
- Day 150: EMA sends the queries on which the EMA responsible committee is seeking input on to GMO CAs for which EMA has a confidentiality agreement on records.
- Day 170: GMO CAs comments are received
- At Day 180 LoOI: Rapporteur and the EMA responsible committee take due account of the input received. However, the content of milestone documents (including LoOI, assessment report, SmPC, PIL, RMP and ERA) is solely decided by the responsible committee.

For procedures under accelerated assessment the above timelines will be adapted to the accelerated assessment time schedule.

Following publication of the EPAR, EMA sends the EPAR e-mail (Form 7) to all consulted GMO CAs to inform them about the publication.

⁵ Article 12(2) of Directive 2001/18/EC and Article 3.3 of Directive 2009/41/EC.

9. Process map(s)/ flow chart(s)



10. Procedure

Step	Action	Responsibility
Presubmission		
1	<p>Consultation is under the responsibility of the Rapporteur. EMA coordinates the consultation under the Rapporteur responsibility and oversight.</p> <p>At presubmission meeting, GMO status is discussed with the applicant. When relevant, the PL sends the information to the the Rapporteur to confirm the GMO status. In case of doubt, the question is brought for discussion at the EMA responsible committee.</p>	PL
Start of procedure		
2	<p>Day 1</p> <p>Send start of procedure Eudralink message (Form 1) to all GMO CAs listed in "list of GMO CAs" with the following attachments:</p> <ul style="list-style-type: none"> • Evaluation timetable (Form 2) • Confidentiality agreement (Form 3) - Not required for CAs that have undertaken an overall confidentiality agreement with EMA. <p>Request from the applicant to provide the information in Module 1.6.2 to be provided to the GMO CA at step 3.</p>	PA
3	<p>Day 80</p> <p>Upon receipt of the Rapporteur's AR, prepare the extract of the assessment of module 1.6.2 and corresponding questions if the Rapporteur has not already provided this as a separate document.</p> <p>In case of specific ERA (to be confirmed by PL): send by Eudralink to the GMO CA, for which EMA has a signed confidentiality statement on record, the following attachments using the consultation eudralink message (Form 4):</p> <ul style="list-style-type: none"> – Module 1.6.2 (to be extracted) – ERA Rapporteur AR (to be extracted from Rapporteur AR by PL) – Consultation Form for medicinal products that contain or consist of GMOs in respect of which a specific ERA has been developed. <p>In case of non-specific ERA (to be confirmed by PL): send by Eudralink to the GMO CA, for which EMA has a signed confidentiality statement on record, the following attachments using the consultation eudralink message (Form 5):</p> <ul style="list-style-type: none"> – Module 1.6.2 (to be extracted) – ERA Rapporteur AR (to be extracted by PL) – Consultation Form for medicinal products that contains or consists of GMO in respect of which there is no specific ERA 	PA
4	<p>Day 110</p> <p>Upon receipt, save GMO CA comments from in DREAM.</p> <p>Verify that comments are being received by the Rapporteur.</p> <p>Compile the 'overview of comments received on the ERA' (Form 6)</p> <p><i>Note: This document is for CAs only and should not be sent to the applicant</i></p>	PA

5	<p>Day 120</p> <p>Ensure that the overview of the LoQ contains a section "III.4 Environmental aspects" as well as, where applicable, the ERA questions.</p> <p>Following the D120 LoQ adoption, send by Eudralink to the consulted GMO CAs the overview of comment document (Form 6): <i>Eudralink message: Thank you message confirming that the comments on ERA Rapporteur AR and suggestions on the risk minimisation measures will be taken into consideration by the relevant committee during the assessment.</i></p>	PL
	<p>Clock stop</p> <p>As soon as possible, and no later than the Day 150 AR, the Rapporteur indicates if there is a need to request additional input from the environmental authorities to address an identified risk and flag it to the PL.</p>	
7	<p>Day 150</p> <p>Upon receipt of the Rapporteur's D150 AR, in case further input from the GMO CAs is needed (to be confirmed by PL);, EMA sends, by Eudralink, to GMO CAs for which EMA has a confidentiality agreement on records the queries on which the EMA responsible committee is seeking input on.</p>	PA
8	<p>Day 170</p> <p>Upon receipt, save GMO CA comments in DREAM. Verify that comments have been received by the Rapporteur. Compile the 'overview of comments received on the ERA' (Form 6) <i>Note: This document is for CAs only and should not be sent to the applicant.</i></p>	PA
9	<p>Day 180</p> <p>Ensure that the LoOI is taking into account the comments from the consulted CAs (to be reflected similarly to the D120 LoQ).</p> <p>Following the D180 LoOI adoption, send by Eudralink to the consulted GMO CAs the overview of comment (Form 6) : <i>Eudralink message: Thank you for your feedback on the environmental assessment of <product>. The comments received will be duly taken into consideration by the [Committee for Advanced Therapies] [Committee for Medicinal Products for Human Use] during the assessment of the marketing authorisation application. For your convenience, an overview of comments received is provided.</i></p>	PL
10	<p>Day 181</p> <p>In light of the Rapporteur's assessment of the written responses reflect the overall assessment and outcome in the CAT/CHMP AR, in the "Scientific Discussion 3.5 Environmental Aspects" and where necessary, ensure appropriate RMMs are described in the SmPC and PL.</p>	PL
11	<p>Day 210</p> <p>Reflect the overall assessment and outcome in the CAT/CHMP AR in the "Scientific Discussion 3.5 Environmental Aspects" and where necessary, ensure appropriate RMMs are described in the SmPC and PL.</p>	PL
	<p>Post-opinion</p>	
12	<p>Following publishing of the EPAR, send the EPAR e-mail (Form 7) to all consulted GMO CAs to inform them about the publication.</p>	PA

11. Records

When completed the electronic version of the documents generated during this procedure are saved in the DREAM Product folder: EDMS\Cabinets\01. Evaluation of Medicine\H-C\A-C\[product]\...

All applicable records are to be filed as described in SOP/PDM/1004.