Ms Rocio Salvador Roldan
Policy Officer
Unit B5- Medicines
Directorate General Heath and Food Security (DG SANTE)
European Commission
Building B232
1049 Brussels
Belgium

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Dear Ms Salvador Roldan

Subject: GMO in the context of clinical trials for ATMPs
Our presentation at the EMA CAT Interested Parties Meeting on 13 September 2018

Firstly, ARM, EBE, EFPIA, and EuropaBio would like to thank the Commission and the Member States for listening to our earlier feedback as well as for the steps that have been taken to address the challenges raised by the GMO related aspects for clinical trials with ATMPs. We appreciate the significant progress that has been made in a relatively short period of time and the efforts made to find an aligned position between some Member States.

The time and resource needed to apply for GMO approval is often an addition to an already lengthy and varied clinical trial application (CTA) approval process for ATMPs across Member States. Further streamlining of the current framework is welcome. In a joint ARM/EBE/EFPIA/EuropaBio position paper published in September 2017, several solutions were proposed and we thank the Commission and Member States for acting on some of these. We trust you will continue to evaluate our medium and long-term proposals including the possibility for voluntary mutual recognition or harmonisation procedures for GMO assessment.

In addition to these proposals and the feedback we shared with you at the EMA CAT Interested Parties meeting on 13 September 2018, we would like to offer the following supplementary comments and proposals for consideration with the relevant Member State competent authorities:

- **More streamlined approach to GMO submission and assessment of ATMPs containing or consisting of GMOs**

  A significant step has been taken by some Member States to reach an agreement on the Questions & Answers, Good Practice and Common Application Form documents. This progress will be limited without a streamlined and consistent approach to implementation across all Member States.

  Eliminate duplication of information across forms and documents required for submission

  The same or very similar information is required in the GMO common application form, the Summary Notification Information Format (SNIF), and some local GMO application forms. Continuing to require duplicate information in multiple format types represents an increase in burden and inefficiency and seems at odds with the intended purpose of this initiative. Additionally, clear implementation timelines should be published. We respectfully request the Member States and the Commission to carefully evaluate the level of duplication between different documents required for submission and to consider whether some forms can be eliminated, adapted or harmonised into a single common form.

Eliminate duplication of information in subsequent submissions for the same product and/or trial site

Efficiency can also be gained in reducing or eliminating duplication in subsequent GMO submissions for clinical trials and/or trial sites (where approval is granted on a site-specific basis) using the same investigational ATMP. Question 3 of the Questions & Answers document suggests that some GMO competent authorities are open to consider the possibility of applying a streamlined procedure in respect of multiple trials with the same product and that this should be discussed with the relevant authority on a case by case basis. We ask the Commission and Member States to consider whether an aligned and more streamlined position could be reached on this point. For example, GMO authorisation could be performed at the product level rather than for each clinical trial or for each site in a clinical trial. Alternatively, submissions for subsequent trials could cross-refer to information provided in previous submissions rather than repeating the same information in an entirely new submission.

Agree a common set of documents required for submission to GMO authorities

Further alignment and agreement on the documents required for submission to GMO authorities would also be a welcome step forward. It would be helpful to generally define which elements of the CTA are relevant for GMO review and approval, including when a multi-site trial is carried out at sites authorised for different GMO classes. For example, core documents pertaining to the clinical trial application (CTA) dossier are requested for some, but not all GMO applications (e.g. Investigator's Brochure, protocol). When a substantial amendment to the initial CTA is made, it is not clear whether the amendment shall be submitted to the GMO authority after initial GMO approval, and when submission is requested, it remains unclear whether this might imply reassessment and potentially re-approval. A harmonised, more streamlined approach to define a substantial change to the GMO dossier in the context of a CTA amendment and avoid duplication of assessments by Clinical Trial and GMO authorities, along with clear processes and timelines, would be very much welcomed.

Agree a common environmental risk assessment and common application form for other product types

Additionally, it would be beneficial to elaborate further guidance and a common application form for other product types. These are currently available for human cells genetically modified by means of retro/lentiviral vectors. Application form and guidance would be needed, for example, to cover both cell-based and vector-based therapies using other types of modified viral vectors (e.g. AAV, HSV, MVA, VV, etc.) as well as genome editing techniques.

- **Additional guidance on interpretation of GMO/GMM Directives (Directive 2001/18/EC and Directive 2009/41/EC) in context of ATMPs**

  Guidance given in the Questions & Answers document that aims at clarifying which products fall within or outside the scope of the GMO legislation is beneficial, and we further encourage the Commission to continue working with the relevant authorities to ensure an aligned position across all Member States.

  The alignment across Member States should be extended to the view on whether a product should be treated as “deliberate release” or “contained use”; it is essential to facilitate a more harmonised and streamlined approach, leading eventually to the possibility of mutual recognition. This determination should seek consistency with and anticipate the requirements for environmental risk assessment of a GMO at the time of marketing authorisation in accordance with Annex 1 of Directive 2001/83/EC.

- **Increased transparency on streamlining the EU GMO framework for ATMPs**

  The GMO framework within Member States can be fragmented with different authorities involved in the authorisation at the national and regional or local levels. In some Member States, for example, where multiple submissions to different authorities are required, it is not clear who can use the agreed common application form for submission to which authority. Feedback from some authorities in

Member States who were signatories to the common application form has been that agreed form is not applicable for submissions made to those authorities. Lack of defined timelines for implementation within each country must also be clarified before sponsors can begin using the documents published. It would be helpful to understand which authorities in each Member State were signatories for the documents published by the Commission. Increased transparency of this information will help ATMP developers and other stakeholders to know who to contact for questions regarding the implementation of the documents published.
Also, in the interest of increased transparency, the identification of a single national point of contact, where this currently does not exist, would facilitate the GMO approval process for ATMPs.

- **Multi-stakeholder workshop on GMO aspects of clinical trials involving ATMPs**

  Reducing the complexity of the current framework requires collaboration and a coordinated effort across different stakeholders impacted by any changes. With this in mind, we encourage the organisation of workshop to discuss the challenges faced by applicants and generate workable solutions within the existing legal framework across relevant stakeholder groups including the Commission, GMO authorities (at Member State national, regional and local levels if applicable), clinical trial authorities, sponsors of clinical trials with ATMPs (e.g. industry, academia, research organizations) and hospitals who are frequently clinical trial sites for these types of products.

  ARM, EBE, EFPIA, and EuropaBio would welcome the opportunity to discuss collaborative solutions to the existing challenges and would be happy to participate in such a multi-stakeholder workshop. We would also be ready to support the Commission in the organisation of such a workshop as needed.

The existing duplications and inefficiencies in the current framework create a burden for all stakeholders involved and will only be exacerbated as the number of ATMPs containing GMOs in development increases. Without further progress to streamline the current GMO framework for ATMPs in the EU, efficient patient access and competitiveness of the EU market as a place for development of these types of novel ATMPs will continue to be hindered.

We trust you will find these comments useful in the ongoing discussions with Member State Competent Authorities for GMOs and Clinical Trials and remain at your disposal if you would like additional clarifications.

We look forward to your response to our proposals to further progress on this important issue.

Yours sincerely,

Annie Hubert
Senior Director, EU Section and Public Policy
ARM

Barbara Freischem
Executive Director
EBE

Sini Eskola
Director, Team Leader
Regulatory, Drug Development & Manufacturing
EFPIA

Bernard J. Grimm
Director Healthcare Biotechnology
EuropaBIO