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## **Possible solutions to improve the European regulatory procedures for clinical trials with Advanced Therapy Medicinal Products consisting of or containing Genetically Modified Organisms**

Advanced therapy medicinal products (ATMPs) are innovative medicinal products which have the potential to bring high transformative value to patients, including potential cures, by either correcting the underlying cause of their disease (e.g. a genetic defect) or by modifying a function in the body to cure or significantly ameliorate their disease. Some ATMPs, such as gene therapies, consist of or contain Genetically Modified Organisms (GMOs). Due to their GMO status, Advanced Therapy Investigational Medicinal Products (ATIMPs) require additional steps in the clinical trial authorisation procedure.

The objectives of this position paper are:

- to summarize the issues faced by sponsors relating to GMO applications currently required in the European Union prior to conducting clinical trials with ATIMPs consisting of or containing GMOs,
- describe how these issues will be further compounded by the introduction of the Clinical Trials Regulation (EU) No 536/2014, and
- propose solutions to improve the application and assessment process and avoid unnecessary delays in patient access to these innovative medicines.

### **Current issues identified with applications for clinical trials with GMOs in the EU:**

As for any clinical trial with an investigational medicinal product, approvals are required from the competent health authorities and from a national or regional Ethics Committee. In the case of ATIMPs consisting of or containing GMOs, an additional approval for the environmental and biosafety aspects of the use and release of the GMO is required by the GMO competent authorities. The GMO application and approval process is lengthy in some Member States and may cause delays of up to 12 months to the authorization to start a clinical trial. Current issues that have been identified can be categorized as follows:

1. EU GMO regulations and directives are not specific to medicinal products:
  - Legislation concerned with GMOs was drafted primarily with plant GMOs in mind with a goal to protect food consumers and crops from contamination. This means that the information requested is not always relevant and that application forms are generally not designed for medicinal products.
  - Agencies for GMO evaluations in Member States can also be responsible for transgenic plants, genetically modified foods and feeds and environmental biosafety, for example, in addition to medicinal products consisting of or containing GMOs, and therefore do not necessarily review the application with a focus on clinical studies in a hospital environment.
  - The authority responsible for review of GMOs is often not the Health Authority and varies between Member States. This can create additional delay because of different timetables for assessment and need for extra communication.

- The current Member State oriented review processes require extensive knowledge at each agency to be able to perform in-depth assessments. With the growth of ATIMP research and the increased complexity of GMO-medicinal products, each Member State authority involved in environmental risk assessment (ERA) reviews will be required to have even more experienced reviewers with a background in healthcare related products.
2. Disparities across Member States in the process and timing required for GMO applications and approvals
- GMO directives have been implemented in different ways by Member States, raising some difficulties for the approval of multinational trials of ATIMPs consisting of or containing GMOs:
- In some EU Member States, the GMO application must be approved before the Clinical Trial Application (CTA) is even submitted, in some after approval of the CTA and in some in parallel. The various interactions required for the CTA and the GMO application for multinational trials are very time consuming, extending to more than a year in some cases, creating a significant burden for clinical trials with gene therapy medicinal products (GTMP) compared to clinical trials involving non-gene therapy medicinal products and more importantly, delaying the access by patients to potentially transformative medicines.
  - In some Member States, the GMO requirements involve interactions with many different entities: the national and/or regional responsible GMO authority, the clinical sites including the investigators and safety officers, the laboratories that will manipulate samples from the patients, the head of the hospital(s), etc. All these interactions may be unnecessarily time-consuming and often unpredictable.
  - National laws often require repetition of the full GMO assessment process for consecutive clinical trials with the same ATIMP in the same indication and/or using the same administration scheme. Similarly, the clinical site agreement process often needs to be repeated.
  - As the applicable requirements in each Member States are, for the most part, only available in the national language, many small and medium-sized enterprises (SMEs) that develop gene therapies feel they are insufficiently informed about the process and requirements in the different Member States.
3. The Environmental Risk Assessment (ERA) carried out by Member States can differ, reaching different conclusions
- For multi-state trials, there can be divergences in classification; for a same trial with the same ATIMP, some Member States will apply the “contained use” requirements while others will apply the “deliberate release” requirements. Furthermore, the terminology used for the classification of GMOs also varies across Member States. This creates confusions, inconsistencies, with additional complexities for the sponsor, resulting in a slowing down of the submission and procedure.
  - The definitions of GMO in the contained use and deliberate release legislation leave some room for different interpretations, creating redundancy and confusion in the application process.

In conclusion, the application process for conducting clinical trials with an ATIMP consisting of or containing a GMO in the EU involves review by different responsible authorities, with additional documents and procedures to the standard CTA review by the competent health authority and the Ethics Committee. A system that involves more efficient review procedure, while taking into account

the specificities of ATIMPs consisting of or containing a GMO, would ensure a shorter and more predictable clinical trial review and approval process.

Moreover, such applications may become even more complicated in the future as to date no system has been foreseen to streamline and harmonize the processes for submission of GMO specific documents with the entry into force of the new Clinical Trials Regulation (EU) No536/2014.

### **Proposed solutions**

ARM, EFPIA, EBE and EuropaBio believe that in order to maintain EU competitiveness for the development of innovative ATIMPs and allow patient access to these important medicines in a timely fashion, the following proposals need to be considered by the European Commission and Member States to address the above stated issues. The near- and medium-term solutions could be implemented quickly to allow streamlining of the assessment for clinical trials that continue to be reviewed under the Clinical Trials Directive, while long-term solutions need to be considered for the transition to the Clinical Trials Regulation.

#### Near-term proposals:

1. Create a centralized source of information (website) where the key requirements for clinical trials with ATIMPs consisting of or containing GMOs are clearly explained. This website could also list the GMO authorities in each Member State, ideally with a link to their webpage and provide clarity with regard to the relevant committees and, ideally, provide a contact point for questions.
2. Reviews of the CTA and GMO applications should be carried out in parallel by the Health and GMO authorities. Where required, Member States should adapt their procedure to allow such parallel review and minimise the time to obtain a clinical authorisation.
3. Request GMO authorities in each Member State to include on their websites a brief description of the GMO application process for clinical trials with ATIMPs consisting of or containing GMOs in their country and provide a contact e-mail. This description should preferably be in English with links to the required documents in national language(s) or English. It should be made clear whether applications in English are accepted (which would be preferable) or not. Such information could then also easily be cross-referenced in the centralized source of information (website) mentioned above.
4. Use of a common application form in all Member States for the environmental assessment by the GMO competent authorities, preferably in English, to facilitate the assessment of ATIMPs consisting of or containing GMOs for use in a clinical trial. Note: A form 'For contained use' has already been developed and proposed by ATMP developers to the European Commission in January 2017 in order to standardize the application to GMO authorities across the different Member States.
5. The European Commission should provide guidance for the clinical trial applications of ATIMPs consisting of or containing GMOs which would lay down the minimum information required from sponsors. This guidance could also explain in which case "deliberate release" and "contained use" applies, based on a harmonized classification and the impact on or consequences for sponsors.

Medium-term proposals:

6. It is recommended that the authority responsible for CTA review within each Member State also acts as the single contact between the sponsor and the relevant national authority responsible for the GMO environmental risk assessment. This model has been successful in Germany since 2015. Enhanced interactions between the health and GMO national competent authorities, for instance by having a health competent authority representative attending meetings or discussions by the GMO competent authority and vice-versa, would also contribute to common understanding and approaches.
7. Similar to the Mutual Recognition Facilitation Group which started in 1995 as an informal group to facilitate marketing authorisations by mutual recognition procedures, or similar to the Voluntary Harmonisation Procedure currently in place for clinical trials, it is suggested that a GMO Facilitation Group composed of GMO authorities across Europe, be created to facilitate dialogue and foster the adoption of more uniform and rapid decisions on GMO aspects of ATIMPs. The implementation of the Clinical Trial Regulation (currently planned for 2019) would constitute a good opportunity to start a dialogue between GMO authorities in the EU Member States that could eventually lead to a voluntary mutual recognition of decisions.

Long-term proposals:

8. Adapt the EU portal to be used with the entry into force of the new Clinical Trials Regulation (EU) No 536/2014 as defined in its article 80 to accommodate the specific requirements of the GMO approval process, for ATIMPs consisting of or containing GMOs.
9. Ensure harmonized content in aspects covered by Part I of the application (as defined by Article 6 of the Regulation (EU) No 536/2014) with the reporting Member State coordinating the review, and limit information in aspects covered by Part II (as defined in Article 7 of the Clinical Trials Regulation) to site-specific information. For that purpose, a dedicated section could be created in 'Add advanced therapy' in Part I and a dedicated section could be created in 'Other documents' in Part II.
10. In line with the Clinical Trials Regulation, we propose the creation of a Regulation for the application process of ATIMPs consisting of or containing GMO. This would be applicable in all EU Member States and would describe the application forms required, the maximum duration for review, and the terminology to be used. The review of the GMO application should be conducted in parallel with the CTA review and coordinated within the Clinical Trials Regulation (EU) No 536/2014. National aspects of GMO applications could still be reviewed by national authorities in a coordinated system with a Reporting Member State. The new Regulation would also confirm the harmonized content in Part 1 and site-specific information in Part 2 as explained under the above-mentioned proposal. The aim of the Regulation would be to harmonize the application process across the EU. It could also provide a template for the application form.
11. Eventually, the application process could evolve into a centralized process for clinical trials conducted with ATIMPs consisting of or containing GMOs. This procedure could leverage the portal put in place for CTAs under the Clinical Trials Regulation (EU) No 536/2014. This would require a modification of the new Regulation proposed above.

ARM, EFPIA, EBE and EuropaBio would welcome any initiative aiming to facilitate the dialogue among the different GMO authorities in the EU Member States and the implementation of the above-mentioned proposals.

### **Conclusion**

Currently there is no harmonized framework for the assessment and approval of ATIMPs consisting of or containing GMOs. The disparity between authorities and requirements at Member State level make applying for clinical trials for such ATIMPs a lengthy and cumbersome exercise. However, the application and approval process will become even more challenging upon the introduction and full implementation of the Clinical Trials Regulation (EU) No 536/2014.

ARM, EFPIA, EBE and EuropaBio would welcome any initiative aiming at facilitating the dialogue among the different GMO authorities in the EU Member States to improve the currently fragmented system and ultimately aiming at developing a framework compatible with the requirements of the Clinical Trials Regulation.

Without the suggested harmonisation and simplifying of the GMO registration process for clinical trials with ATIMPs consisting of or containing GMO, it will be difficult for developers to leverage the advantages of the improved Clinical Trials Regulation. On the contrary, it may act as a disincentive for companies to conduct clinical trials with ATIMPs consisting of or containing GMOs in the European Union.

The access by patients to new medicinal products, in particular when these are potentially curative or transformative, should be facilitated and the review time for clinical trials applications optimized without compromising the patient and environmental safety. The proposed solutions would help to ensure that development of such innovative medicines is facilitated and unnecessary delays are avoided.

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Note: A longer version of this position paper, with additional background information and details is available here:

[https://alliancerm.org/sites/default/files/Position\\_paper\\_ARM\\_EFPIA\\_EBE\\_EuropaBio\\_27Sept17\\_longversion.pdf](https://alliancerm.org/sites/default/files/Position_paper_ARM_EFPIA_EBE_EuropaBio_27Sept17_longversion.pdf)

**About the Alliance for Regenerative Medicine:**

The Alliance for Regenerative Medicine (ARM) is an international multi-stakeholder advocacy organization that promotes legislative, regulatory and reimbursement initiatives necessary to facilitate access to life-giving advances in regenerative medicine and advanced therapies worldwide. ARM also works to increase public understanding of the field and its potential to transform human healthcare, providing business development and investor outreach services to support the growth of its member companies and research organizations. Today, ARM has more than 250 members and is the leading global advocacy organization in this field. To learn more about ARM or to become a member, visit <http://www.alliancerm.org>

**About EBE:**

European Biopharmaceutical Enterprises (EBE) represents the voice of biopharmaceutical companies of all sizes in Europe and is a specialised group within the European Federation of Pharmaceutical Industries and Associations (EFPIA). Established in 2000, EBE is recognised as the leading biopharmaceutical association in Europe.

To learn more about EBE, visit: <http://www.ebe-biopharma.eu/>

**About EFPIA:**

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the pharmaceutical industry operating in Europe. EFPIA is the voice on the EU scene of 1,900 companies committed to researching, developing and bringing to patients new medicines that will improve health and the quality of life around the world. To learn more about EFPIA, visit: <https://www.efpia.eu/>

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EuropaBio, the European Association for Bioindustries, promotes an innovative and dynamic European biotechnology industry. EuropaBio and its members are committed to the socially responsible use of biotechnology to improve quality of life, to prevent, diagnose, treat and cure diseases, to improve the quality and quantity of food and feedstuffs and to move towards a bio-based and zero-waste economy. Our members are involved in research, development, testing, manufacturing and commercialisation of biotechnology products and processes and have a wide range of activities: human and animal health care, diagnostics, bio-informatics, chemicals, crop protection, agriculture, food and environmental products and services. EuropaBio represents 80 corporate and associate members and bioregions, and 17 national biotechnology associations in turn representing over 1800 biotech SMEs.

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