

27 September 2017

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

1. Introduction

The objectives of this position paper are to:

- Summarize the issues faced by sponsors relating to Genetically Modified Organisms (GMOs) applications which are currently required in the European Union prior to conducting clinical trials with Advanced Therapy Investigational Medicinal Products (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
- Propose solutions to improve the application and assessment process in order to support European competitiveness with regard to biomedical innovation, including ATIMPs in both the near term and long term and avoid unnecessary delays in patient access to these innovative medicines.

2. Background

Advanced Therapy Medicinal Products (ATMPs) such as Gene Therapy medicinal products (GTMPs) 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.

The European Union (EU) created the Advanced Therapy Medicinal Product (ATMP) Regulation in 2007¹ to detail specific registration considerations for ATMPs that comprise somatic cell therapy medicinal products, tissue engineered products, and gene therapy medicinal products. The European Medicines Agency (EMA) has now approved 8 ATMPs, four of which are either gene therapy or cell therapy products containing genetically modified cells (Glybera®, Strimvelis®, Zalmoxis® and Imlygic®). This number is higher than in other regions of the world and thereby, a relatively positive environment for further development of new gene therapies or other types of ATMPs consisting of and/or containing GMOs has been created in Europe. Examples of approved gene therapy products include hematopoietic stem cells or T cells that are genetically modified *ex-vivo* with a lentiviral vector or a gamma retroviral vector, and *in-vivo* gene therapies with adeno-associated viral vectors administered via local or systemic administration.

¹ REGULATION (EC) No 1394/2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

As for any new medicine, well-designed and adequately controlled clinical trials to demonstrate the safety and efficacy of ATMPs consisting of or containing GMOs must be conducted prior to their approval. However, due to their GMO status, these products require additional steps in the clinical trial authorisation procedure as outlined below.

For each clinical trial application, there are three levels of review, which are often performed by separate national agencies:

1. Standard review of a Clinical Trial Authorisation (CTA) application, regulated under Directive 2001/20/EC, which in the EU is a national Member State responsibility (although this will change with the revised Clinical Trials Regulation² expected to come into force in 2019).
2. Ethics review, through which specific issues relating to the use of the GMO are commonly assessed. EU Member States normally assign this review to national or regional agencies with specialist expertise in gene therapies.
3. Additionally, and specifically for products consisting of or containing a GMO, a review of the environmental and biosafety aspects of the use/release of the GMO.

The latter requirement is a complicating factor since these assessments are based on GMO legislation (detailed below) which is designed mainly to cover crops and animal genetic modification rather than medicinal products.

In addition, and most importantly, the recent adoption of the Clinical Trials Regulation² aiming at facilitating the conduct of clinical trials in the European Union and which sets out to harmonize clinical trial requirements across the EU, does not cover the additional requirements associated with GMO assessments. Therefore, concern is now being raised as to how it will be possible to obtain these national approvals once the new legislation is fully adopted.

The issues relating to the cumbersome and lengthy processes for completing GMO application were discussed in May 2016 during an EMA workshop to explore solutions to foster development of ATMPs³. This workshop included participation of multiple stakeholders, including national competent authorities, the European Commission, small and large companies, as well as leading academics and researchers, patients and healthcare professionals' organizations, etc.

The topic of GMO applications was also discussed during a dedicated meeting at the European Commission on 8 November 2016 and a conference co-sponsored by EMA and the European Biopharmaceutical Enterprises (EBE) on 16 December 2016 (ref: EMA/853948/2016).

² REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use

³ Report EMA/345874/2016. Advanced therapy medicines: exploring solutions to foster development and expand patient access in Europe. Outcome of a multi-stakeholder meeting with experts and regulators held at EMA on Friday 27 May 2016.

3. Existing regulations for the GMO review process

The main pieces of legislation applying to ATIMPs consisting of or containing GMOs⁴ are:

- Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms;
- Directive 2009/41/EC on the contained use of genetically modified micro-organisms;
- Regulation (EC) 1946/2003 on transboundary movements of genetically modified organisms.

The two Directives have been implemented in the national legislation in each Member State with significant differences between Member States. This has the effect of different documentation request and different review and approval frameworks between the Member States.

For example, according to Article 2 of Directive 2001/18/EC, a genetically modified organism (GMO) is defined as follows: *"an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination."*

And in accordance with the same Directive, an "organism" is defined as: *"any biological entity capable of replication or of transferring genetic material"*.

Thus, while some gene therapies are by definition GMOs, the applicability of this definition to other gene therapy products, such as genetically modified cells, is not obvious. However, without a clear derogation from the GMO Directives, all such products need to follow both the medicinal products and GMO legislations.

The legislation leaves some room for interpretation and for multi-state trials, there can be dissimilarities in classification by Member States as 'contained use' or 'deliberate release' regulations or in the definition of GMO. This creates some difficulties for applicants in the authorization of multinational clinical trials as outlined below.

4 – Current issues identified with applications for clinical trials with GMOs in the EU

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 GMO 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 are not

⁴ Supplemented by:

- [Regulation \(EC\) 1829/2003](#) on genetically modified food and feed
- [Directive \(EU\) 2015/412](#) amending Directive 2001/18/EC as regards the possibility for the Member States to restrict or prohibit the cultivation of GMOs in their territory
- [Regulation \(EC\) 1830/2003](#) concerning the traceability and labelling of genetically modified organisms and the traceability of food and feed products produced from genetically modified organisms.

always relevant and that application forms are generally not designed for medicinal products, leading to inefficiencies and inconsistencies in the approach taken by different applicants.

In addition, 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. As a consequence, 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:

- As mentioned above, the authority responsible for GMO approval may be different to the agency responsible for Clinical Trial Authorisation (CTA). In some EU Member States, the GMO application must be approved before the CTA is even submitted, in some after approval of the CTA and in some in parallel. The various interactions required for the CTA and GMO application for multinational trials are very time consuming. In addition, there are often no timelines for the assessment and approval by GMO authorities making it difficult for developers to plan ahead. As the CTA review for ATIMPs, including gene therapy medicinal products (GTMPs) is already longer than for conventional Investigational Medicinal Products (IMPs) (up to 180 days with current legislation), adding the GMO applications can sometimes make the entire process extend to more than a year. This creates a significant burden for clinical trials with GTMPs compared to clinical trials involving non-gene therapy medicinal products and more importantly, this delays the access by patients to potentially transformative medicines. Examples of the varying national pathways are shown in Figure 1 below.

Of note, France has recently changed its process for reviewing and approving clinical trials with ATIMPs consisting of or containing GMOs. Prior to May 2017, as illustrated in Figure 1, the CTA could not be submitted to the French Health Authority (ANSM) before the approval by the GMO authority (HCB), leading to long approval times. Recently, changes have been implemented so that the reviews by the Health and the GMO Authorities can be carried out in parallel. Such a change represents a great improvement as clinical trials could start much earlier, meaning that patients could have earlier access to ATIMPs whilst maintaining the rigorous regulatory review for safety requirements.

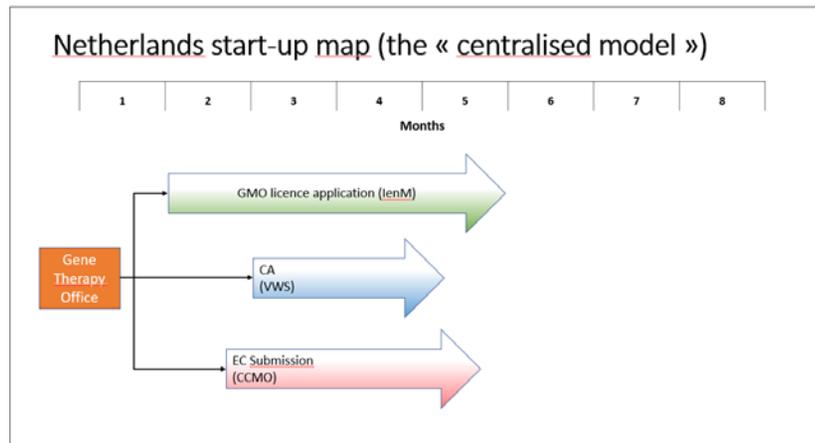
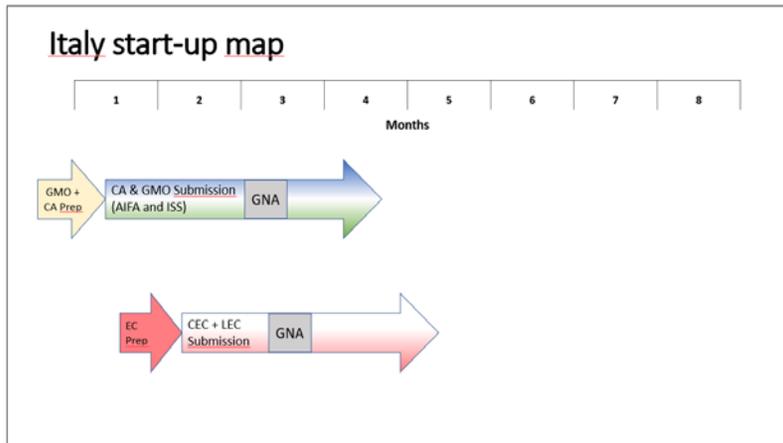
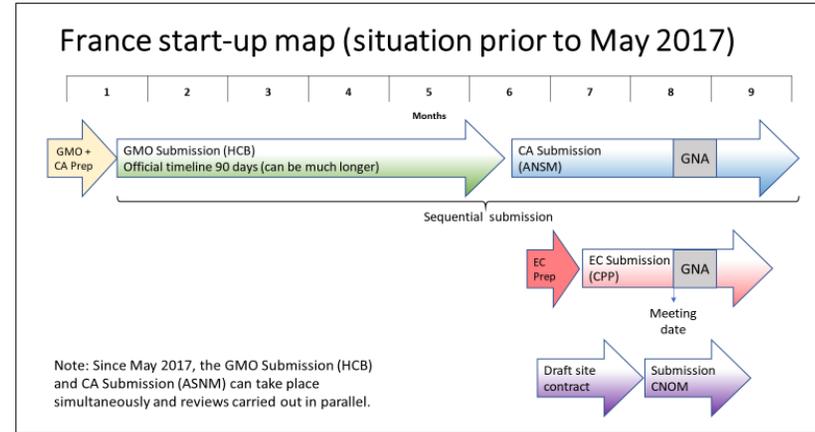
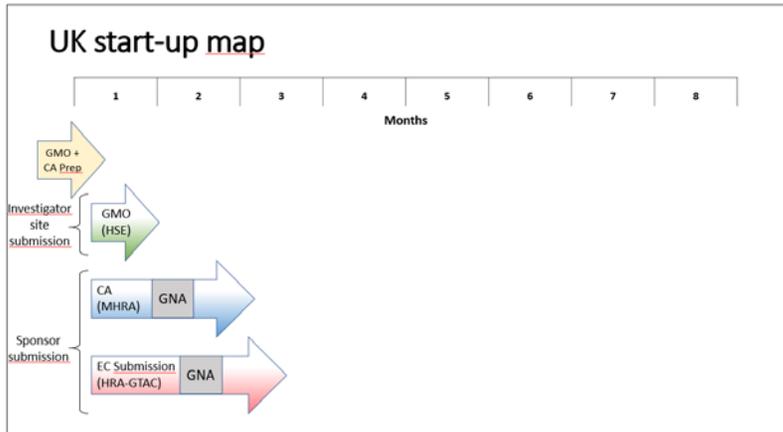
- In some countries, the GMO requirements involve interactions with many different entities: the national and/or regional responsible GMO authority, the clinical sites including the investigators and safety officers, the laboratories that will manipulate samples from the patients, and the head of the hospital(s), and sometimes communication with the Ministry of Finance to pay the appropriate fee. 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 for each clinical trial. All these steps contribute to delays before clinical trials can be initiated.
 - In some Member States, there are varying in-country regional requirements that apply and thus several GMO applications may need to be fulfilled in a single country.
 - 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. Divergences in classification within a same national authority are also possible depending on when and by whom the application is reviewed. Furthermore, the terminology used for the classification of GMOs also varies across Member States and can create confusion (for example for the level of biosafety required for the contained use: L1, L2, L3 or R1, R2, R3 etc.). This creates inconsistencies, with additional complexities for the sponsor and 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 on whether some products need to follow both the medicinal product and the GMO legislations. In the case of genetically modified cells, some countries consider that both the viral vector (a starting material in ex vivo transductions) and the genetically modified cells (the drug product) are GMOs, whereas other countries consider that only the viral vector is a GMO, creating redundancy and confusion in the application process, where it is unclear if the forms need to be filled in twice.

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 in addition to the standard CTA review by a competent health authority and the Ethics Committee. Such reviews require expertise and understanding of the information related to ATIMPs in the application. 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. Reducing the GMO application review to one per product and per GMO authority would also facilitate the start of clinical trials that use the same ATIMP and would eliminate risk of discordance in the classification of the same product.

Moreover, such application 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) No 536/2014.

Figure 1: Examples of national processes for clinical trials application for gene therapy medicinal products



(GNA: Ground for Non-Acceptance)

Note: In practice, timings can be much longer than those indicated here.

5 – Proposed solutions

ARM, EFPIA, EBE and EuropaBio believe that in order to maintain EU competitiveness for the development of innovative ATMPs and allow patient access to these important medicines in a timely fashion, the following proposals, listed by near-, medium-, and long-term categories, 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 as we 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 ATMPs consisting of or containing GMO 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 the GMO authorities. Where required, Member States should adapt their procedure to allow such parallel review and minimise the time to obtain a clinical trial 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 ATMPs 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 ATMPs consisting of or containing GMOs to be used 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 the GMO authorities across the different Member States (see Appendix).
5. The European Commission should provide guidance for clinical trial applications of ATMPs 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 or regional authority responsible for the GMO environmental risk assessment. This model has been used successfully 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 Trials 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.

6 – 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 GMOs, it will be difficult for developers to leverage the advantages of the improved Clinical Trials Regulation and 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.

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/>

About EuropaBio:

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. Read more about our work at www.europabio.org.

APPENDIX
APPLICATION FORM PROPOSED FOR THE ASSESSMENT OF THE CONTAINED USE
CLASSIFICATION APPLIED TO ATIMPs CONSISTING OF AND/OR CONTAINING GMOs
(proposed as a follow-up of a meeting held at the European Commission on 8 November 2016)

FORM XX: ASSESSMENT OF THE CONTAINED USE CLASSIFICATION APPLIED TO ADVANCED THERAPY INVESTIGATIONAL MEDICINAL PRODUCTS CONSISTING OF AND/OR CONTAINING GENETICALLY MODIFIED ORGANISMS

VERSION 1.0 (January 2017)

SCOPE & BACKGROUND

As part of the approval of an investigational medicinal product consisting of and/or containing genetically modified organisms (GMOs) for use in a clinical trial, Sponsors are required to comply with legislation for contained use of a GMO (Directive 2009/41/EC) or should contained use not be relevant, with legislation for the deliberate release into the environment of GMOs (Directive 2001/18/EC).

This form is solely intended to support clinical trial authorisation (CTA) applications for clinical studies to be conducted within EU Member States using advanced therapy investigational medicinal products (ATIMPs). This will include both gene therapy medicinal products and somatic cell therapy medicinal products that are subject to genetic modification, as defined in Regulation (EC) 1394/2007 and Directive 2009/120/EC. This application form applies only for the assessment of the classification of the use of ATIMPs under contained use.

The GMO may constitute the active substance, such as a viable viral vector, or may be a (potential) residual component of the final medicinal product, such as a viral vector used to transduce cells. For the purpose of this application, genetically modified human cells should be considered as GMOs.

The information provided in this form shall be used by the relevant authorities within each Member State to assess the proposed clinical trial in accordance with Directive 2009/41/EC and confirm that the authority agrees with the proposed use of the GMO at the proposed sites for this study. The Member State may request additional information to supplement this assessment, as required.

Sections A and E contain general information regarding the use of the GMO in this study. A Member State, in the interests of transparency, may publically disclose this information. Sections B, C and D contain additional details required by environmental authorities for assessment and will not be publically disclosed. In the event that information in Section, B, C or D was intended for public disclosure, this would require the consent of the Applicant.

Section	Description	Comment	Category
A	General Information	May be publically disclosed	Open
B	Details of the GMO components	Should remain confidential.	Closed
C	Safety Measures to Protect Humans and the Environment from Unintentional GMO Exposure	Should remain confidential.	Closed
D	Conclusions of Safety Measures to Protect Humans and the Environment from Unintentional Exposure to GMOs	Should remain confidential.	Closed
E	Overall Assessment of GMO Classification	May be publically disclosed	Open

A. GENERAL INFORMATION

DETAILS OF APPLICATION

a) Member State(s) in which investigational use of the medicinal product is intended <i>List member states</i>	
b) Member State(s) applied to <i>previously</i> for investigational use of the medicinal product (if applicable) <i>List member states</i>	
Member State	Contained use risk classification given (if applicable)
c) Reference number <i>To be inserted by authorities in each Member State (MS)</i>	
d) Name of the drug product (ATIMP) (INN/proposed INN; if available commercial name or current sponsor code)	
e) Type of product <i>Use the ATMP definition as stated in Regulation EC 1394/2007</i>	
f) Proposed clinical trial:	
EudraCT Number (if available)	Trial name, protocol number and therapeutic indication
g) Date of acknowledgement of application <i>To be inserted by authorities in each MS</i>	

APPLICANT DETAILS

a) Name of Applicant <i>State the name of the Sponsor or other responsible applicant.</i>
--

<p>b) Address of Applicant</p> <p><i>This should be consistent with the name provided.</i></p>	
<p>c) Details of Applicant</p> <p>(i) Sponsor / Third Party (delete as applicable)</p> <p>(ii) Address of Sponsor (if different from Applicant)</p>	
Responsibility	Legal Entity Name and Address

GENETICALLY MODIFIED ORGANISM(S)

<p>Indicate the name and nature of each type of GMO contained in the medicinal product</p> <p><i>Briefly describe each GMO contained in the medicinal product, such as gamma retroviral vector, or genetically modified human cell and the component type, such as active substance.</i></p>	
GMO Description	Component Type

GMO(S) – PARENTAL ORGANISM(S)

<p>Indicate the name and nature of each type of GMO contained in the product</p> <p><i>Briefly describe each GMO, using the description from above and state the parental organism, such as Moloney Murine Leukaemia Virus</i></p>	
GMO Description	Parental Organism

CLINICAL SITES FOR ADMINISTRATION OF THE ATIMP

Clinical sites within the EU to which the medicinal product is intended to be administered to patients under the terms of the clinical trial authorisation applied for

Please ensure that the Member State is evident in the Site Address.

Clinical Site Name	Site Address	Country

B. Details of the GMO components and the GMO clinical contained use application

1. GENERAL DESCRIPTION OF THE ATIMP

<p>a) Description of the medicinal product as supplied</p> <p><i>Provide a description of the final product as supplied to the clinical site.</i></p> <div style="border: 1px solid black; height: 60px; margin-top: 5px;"></div>								
<p>b) Site(s) of Manufacture and testing</p> <p><i>List the sites which perform manufacturing operations, including testing sites</i></p> <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 5px;"> <thead> <tr> <th style="width: 33%;">Site name</th> <th style="width: 33%;">Site Address</th> <th style="width: 33%;">Manufacturing Operations</th> </tr> </thead> <tbody> <tr> <td style="height: 20px;"></td> <td></td> <td></td> </tr> </tbody> </table>			Site name	Site Address	Manufacturing Operations			
Site name	Site Address	Manufacturing Operations						

c) Description of constituent components of GMO

A GMO product is usually constructed from a donor organism, containing the selected genes intended to be transferred, with the help of a vector; and a recipient organism and/or parental micro-organism(s).

List donor organism, recipient organism and/or parental micro-organism(s) and all other components of the GMO and provide description of source (origin) and function. For viral vectors, this should be a listing of the constituent components of the viral genome and for genetically modified cells, include e.g. a listing of the provirus, transposon or similar. For origin, also add database identifier, where possible. For description, briefly describe the component's function in the GMO. Duplicate this table for each additional GMO.

GMO name e.g. lentiviral vector

Component Name	Origin	Description
Recipient organism		
Donor organism		
Parental micro-organism(s), if applicable		
Other component		

d) Positional Relationship of Components

Where possible, provide a schematic representation of the components listed above to show positional relationship, e.g. as a map. Add a schematic for each GMO.

e) Biological characteristics of the GMO

Provide any known information regarding potential for integration, replication, recombination, tropism, persistence and latency, dissemination with the GMO. These biological characteristics can be supported by pre-clinical or clinical data with the GMO or similar products in the same class already used (e.g.: bio-distribution, shedding studies)

Biological characteristic	Known information
<i>E.g.: Tropism</i>	<i>E.g.: BD data: XXX bio-distributed only to organ XX and organ XX in pre-clinical model XX</i>

C. Application of Safety Measures to Protect Human Health and the Environment

1. DESIGN OF GMO

The GMO components that form the final ATIMP should be designed to protect the safety of human subjects that take part in the trial (intended recipients). Describe all design features of GMO relevant to human safety and details of risk assessment carried out. For example self-inactivation (SIN) for retroviral vectors. Risk Mitigation Intent should describe the intention of the feature such as prevention of formation of replication component retroviral for SIN and Risk assessment should conclude the current likelihood of the risk. Duplicate this table for each additional GMO. Details of any additional testing and manufacturing steps that support the safety of the GMO should be provided in supporting information.

Design feature	Risk Mitigation Intent	Risk assessment e.g. negligible, low, medium or high

MANUFACTURE, TRANSPORTATION, ADMINISTRATION AND DISPOSAL OF GMO

a) Potential Exposure to Non-Patients (unintended human recipients)

The safety measures described in C1 may also apply to non-patients (unintended human recipients). However, as part of the contained use assessment, the risk of exposure of non-patients to the GMO should be minimised. Describe key steps in the manufacture, transportation, administration and disposal of the GMO relevant to human safety and details of risk assessment carried out. Risks should only be considered by a given Member State(MS), if the activity that exposes humans to that risk takes place within that MS. There are 4 tables, one each for each aspect. Add rows as required. Initial text has been provided for guidance but should be revised as appropriate.

Manufacturing operations at clinical site / Preparation operations at clinical site	Potential risk	Safety measures and mitigation of risks	Risk assessment e.g. negligible, low, medium or high
Manufacture	<i>Release of GMO in preparation area resulting in site staff exposure.</i>		

Step	Potential risk	Safety measures and mitigation of risks	Risk assessment e.g. negligible, low, medium or high
Transportation	<i>Release of GMO to from the packaging resulting in multiple risks of exposure such as courier and HCPs.</i>		

Step	Potential risk	Safety measures and mitigation of risks	Risk assessment e.g. negligible, low, medium or high
Administration	<i>Needle-stick injuries whereby GMO is accidentally transmitted to HCPs</i>		

Step	Potential risk	Safety measures and mitigation of risks	Risk assessment e.g. negligible, low, medium or high
Disposal	<i>Release of viable GMO during disposal resulting in exposure of handlers or cleaning staff.</i>		

b) Potential Environmental Exposure

In addition to protecting human safety, environment exposure should be minimised as part of the contained use assessment. Describe key steps in the manufacture, transportation, administration and disposal of the GMO relevant to environmental risk and details of risk assessment carried out. Risks should only be considered by a given MS if the activity that exposes the GMO to the environment takes place within that MS. There are 4 tables, one for each aspect. Add rows as required. Further tables may be added e.g. for storage, if required. Initial text has been provided for guidance but should be revised as appropriate.

Step	Potential risk	Safety measures and mitigation of risks	Risk assessment e.g. negligible, low, medium or high
Manufacture	<i>Release of GMO in manufacturing facility resulting in release to the environment.</i>		

Step	Potential risk	Safety measures and mitigation of risks	Risk assessment e.g. negligible, low, medium or high
Transportation	<i>Release of GMO to from the packaging resulting in release to the environment.</i>		

Step	Potential risk	Safety measures and mitigation of risks	Risk assessment e.g. negligible, low, medium or high
Administration	<i>Release of GMO during the administration procedure resulting in release to the environment.</i>		

Step	Potential risk	Safety measures and mitigation of risks	Risk assessment e.g. negligible, low, medium or high
Disposal	<i>Release of viable GMO during disposal resulting in release to the environment.</i>		

D. Conclusions of Application of Safety Measures to Protect Humans and the Environment

1. IMPACT OF THE PRODUCT ON HUMAN RECIPIENTS

The Applicant should provide the conclusion of the measures and risk assessments as listed in Section C to eliminate or minimise risk associated with:

- i) Exposure of the GMO to humans
- ii) Impact of any exposure on humans

2. ENVIRONMENTAL IMPACT OF THE PRODUCT

The Applicant should provide the conclusion of the measures and risk assessments as listed in Section C to eliminate or minimise risk of:

- i) Exposure of the GMO to the environment
- ii) Impact of any exposure to the environment

E. OVERALL ASSESSMENT OF GMO CLASSIFICATION

1. STATEMENT OF COMPLIANCE WITH CONTAINED USE LEGISLATION

Applicant should provide a statement confirming both eligibility for, and compliance with, the contained use legislation, as applied in the EU under Directive 2009/41/EC.

2. CONTAINED USE CLASSIFICATION PROPOSED BY APPLICANT

Risk classification applied to GMO (as determined by impact on human subjects and the environment).

GMO	Classification (1-4)

Contained use classes:

Class 1 - activities of no or negligible risk, that is to say activities for which Level 1 containment is appropriate to protect human health and the environment.

Class 2 - activities of low risk, that is to say activities for which Level 2 containment is appropriate to protect human health and the environment.

Class 3 - activities of moderate risk, that is to say activities for which Level 3 containment is appropriate to protect human health and the environment.

Class 4 - activities of high risk, that is to say activities for which Level 4 containment is appropriate to protect human health and the environment