ANSES Opinion
Request No. 2022-AUTO-0167

The Director General

Maisons-Alfort, 9 October 2024

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on the development of guidelines for assessing the environmental risks associated with the deliberate release of medicinal products for human or veterinary use containing or consisting of genetically modified organisms

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.
It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).
Its opinions are published on its website. This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 9 October 2024 shall prevail.

On 26 September 2022, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) issued an internal request to draw up guidelines for assessing the environmental risks associated with the deliberate release of medicinal products for human or veterinary use containing or consisting of genetically modified organisms (GMOs).

French Agency for Food, Environmental and Occupational Health & Safety
14 rue Pierre et Marie Curie, 94701 Maisons-Alfort Cedex
Tel +33 (0)1 49 77 13 50 — www.anses.fr

1. BACKGROUND AND PURPOSE OF THE REQUEST

On 1 January 2022, pursuant to Order No. 2021-1325 of 13 October 2021 and Decree No. 2021-1905 of 30 December 2021, ANSES took over the missions of the High Council for Biotechnology (HCB) relating to the assessment of risks to the environment and public health of all uses of biotechnologies in the open environment, whether relating to plants, animals, micro-organisms or medicinal products.

These missions include environmental risk assessment (ERA) of the deliberate release of medicinal products for human or veterinary use containing or consisting of GMOs.

Guidance documents and discussion papers on assessing the environmental risks of GMO medicinal products are available at European Union (EU) level, enabling applicants among others to identify the information needed for compiling their dossiers and complying with the methodology expected by the European Medicines Agency (EMA), in particular.

In addition to these documents, simplified "common application forms" have been drawn up at EU level and approved at national level, in particular for authorisation applications relating to certain categories of GMO medicinal products for human use.

However, this body of documents governing the assessment of the risks associated with the deliberate release of GMOs into the environment remains fairly general and non-binding. ANSES therefore decided to issue an internal request (see the decision in **Annex I**), in order to hold a discussion on drawing up assessment grids that are as comprehensive as possible, tailored to each type of product and current technical possibilities.

The ANSES guidelines for these assessment grids are intended to be applicable to the various types of authorisation applications associated with the deliberate release of medicinal products for human or veterinary use containing or consisting of GMOs, paying particular attention to the analysis methods expected in support of the ERA.

The scope of these guidelines concerns the risks to health (excluding those to the organism benefiting from the medicinal product) and the environment associated with the use of medicinal products for human or veterinary use containing or consisting of GMOs. Risks to the safety of patients or animals treated with this type of medicinal product do not fall within the remit of the ERA and are not addressed in this opinion or concerned by these guidelines.

It should also be noted that the overall assessment report on the authorisation application dossier – including the part relating to the ERA – is drawn up under EMA's responsibility at European level. In France, when not covered by a centralised procedure, the assessment, authorisation and management of health products are the responsibility of the French Agency for Veterinary Medicinal Products (ANMV) for veterinary medicinal products, and the French National Agency for Medicines and Health Products Safety (ANSM) for medicinal products for human use.

The environmental risk assessment concerns the following types of authorisation applications for medicinal products containing GMOs:

- centralised applications for marketing authorisation (MA) for medicinal products containing or consisting of GMOs under Regulation (EC) No 726/2004 (medicinal products for human use), Regulation (EU) No 2019/6 (veterinary medicinal products) and Directive 2001/18/EC;

- applications for clinical trials of veterinary medicinal products taking place in France that contain or consist of GMOs, in accordance with Articles R. 533-8 and R. 533-22 of the French Environmental Code;
- applications for early access authorisations (EAAs) or compassionate access authorisations (CAAs) for medicinal products for human use containing or consisting of GMOs;
- applications for authorisation of advanced therapy medicinal products prepared on an ad hoc basis (MTI-PP), in accordance with Article R. 533-49 of the Environmental Code;
- applications for the use of GMOs in a contained environment, in the event of doubts about possible release into the environment raised by the CEUCO[1].

Application of these guidelines is therefore intended to be limited to the cases mentioned above, for which ANSES's opinion is required. In this respect, ANSES points out that it is only sent a part of the authorisation application dossiers (the part relating to the environmental risk assessment).

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French Standard NF X 50-110 "Quality in Expert Appraisals – General requirements of Competence for Expert Appraisals (May 2003)".

ANSES entrusted examination of this internal request to an ad hoc Working Group (WG), hereinafter referred to as the "GL-MED-GMO" WG, which has reported to the Expert Committee on "Biotechnologies" (CES BIOTECHS) since 1 February 2024. The CES BIOTECHS was responsible for endorsing all the work. The expert appraisal work also fell within the areas of competence of the Biotechnology Working Group (BIOT WG – until January 2024).

The GL-MED-GMO WG's expert appraisal work was submitted to the BIOT WG on 16 November 2022, 16 March 2023 and 13 April 2023, examined by the CES BIOTECHS on 11 March 2024 and validated by this CES on 9 April 2024.

The collective expert appraisal was conducted on the basis of the guidance documents and discussion papers available at national and European levels, the opinions and comments on authorisation application dossiers previously issued by the HCB and ANSES, as well as by the other EU Member States, and the opinions and comments formulated by EMA on these same dossiers.

To supplement this analysis, the GL-MED-GMO WG deemed it necessary to hold hearings with officials or representatives of the assessment agencies or committees (ANMV, ANSM, CEUCO), and with stakeholders identified as being within the scope of this internal request. The interviewees are listed in **Annex II**.

ANSES analyses interests declared by experts before they are appointed and throughout their work, in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.

The experts' declarations of interests are made public via the website: https://dpi.sante.gouv.fr/.

[1] CEUCO: Expert Committee on contained uses of GMOs, reporting to the Ministry of Research

3. ANALYSIS AND CONCLUSIONS OF THE WG AND THE CES

3.1. Work methodology

The aim of this work was to clarify the requirements and make recommendations on the data to be provided by applicants as part of the health and environmental risk assessments relating to applications for authorisation of medicinal products for human or veterinary use containing or consisting of GMOs.

In order to draw up guidelines for assessing the environmental risks associated with the deliberate release of medicinal products containing GMOs, the GL-MED-GMO WG initially compiled and analysed a body of literature containing all the regulatory and guidance documents relating to its work topic of which it was aware. This body of literature is presented in **Annex III**. This Annex gives the respective scopes of the documents analysed, as well as a grading of their interest or importance in the scope or preparation of the environmental risk assessment (ERA) dossier.

Following an analysis of the body of literature, the GL-MED-GMO WG decided to base its guidelines and recommendations on:

- the common application forms provided by the European Commission for medicinal products for human use (genetically modified (GM) viral vectors, GM adeno-associated viral (AAV) vectors, GM cells);
- Annex IIIA of Directive 2001/18/EC of the European Parliament and of the Council for veterinary medicinal products.

In addition to the body of literature previously established, the GL-MED-GMO WG based its recommendations on the application dossiers previously processed by the HCB and ANSES's BIOT WG, considering their content and the comments made during their assessment. Where information was available, comments issued by other EU Member States and by EMA, or the applicants' responses to these comments, were taken into account.

In order to supplement its analysis, the GL-MED-GMO WG also conducted two series of hearings, whose main objectives were:

- for the first series of hearings, to ensure the exhaustiveness and scope of the documents gathered within the body of literature, and to understand any specific features of the different types of dossiers that may be submitted to ANSES for assessment;
- for the second series of hearings, to ensure the relevance and feasibility of the WG's recommendations.

The frameworks and minutes of the hearings, presented in agreement with the interviewees, are provided in **Annex IV**.

Lastly, a request was sent to EFSA's Focal Point Network[2], which was relayed to all the institutions in the network, to determine whether any similar approach had been followed to discuss or draft guidelines on medicinal products containing GMOs and might therefore be taken into account as part of this work.

[2] EFSA has a national focal point (FP) in each Member State, most often at the national risk assessment agency. These focal points act as an interface between EFSA and the national food safety authorities, research institutes and other stakeholders.

The following request was therefore sent to EFSA's Focal Point Network: "*According to Directive 2001/18/EC of the European Parliament and of the Council on the deliberate release into the environment of genetically modified organisms, EU member states are given the opportunity to communicate comments to the EMA on the environmental risk assessment report provided by companies willing to place medicinal products containing GMOs on the market. In this context, the French agency for food, environmental and occupational health and safety is willing to elaborate guidelines to ease the management of these dossiers and complete the available EMA guidelines with technical requirements. We thus would like to know if other EU countries have conducted a similar approach, or refer to guidelines other than the ones provided by the EMA to applicants in order to formulate their comments.*"

The respondents to this request replied that they had not held any discussions similar to those carried out by the GL-MED-GMO WG, and that they had based their work solely on the common application forms and European guidelines already identified by the WG. The request sent and the list of countries consulted are provided in **Annex V**.

3.2. Guidelines for assessing the environmental risks associated with the deliberate release of medicinal products containing or consisting of GMOs

The guidelines drawn up by the GL-MED-GMO WG for different types of medicinal products containing or consisting of GMOs, and where appropriate a justification for these requests for clarification or recommendations, are annexed to this opinion:

GL-MED-GMO WG's guidelines	Annexes
Guidelines for assessing medicinal products for human use containing genetically modified replicating viral vectors	**Annex VI**
Guidelines for assessing medicinal products for human use containing genetically modified adeno-associated viral vectors	**Annex VII**
Guidelines for assessing medicinal products for human use containing genetically modified cells	**Annex VIII**
Guidelines for assessing veterinary medicinal products containing genetically modified organisms	**Annex IX**

The GL-MED-GMO WG reiterates the following points in particular:

- Concerning the possible **integration of the parental virus into the genome** of the patient or animals, the GL-MED-GMO WG considers that knowledge of this characteristic is needed for assessing the capacity for and ease of release of the GMO, particularly in the event of co-infection with other viruses with which recombination may be possible, and should be included in the ERA.
- Concerning the **contamination of medicinal products by replication-competent viruses** (including the emergence of replication-competent viruses during the production process), where applicable, applicants generally provide a literature review without any real assessment in the context of the GMO medicinal product. The GL-MED-GMO WG proposes that broader discussions be held with the French and European bodies responsible for assessing these medicines, in order to define the

appropriate tests to be carried out, given the importance of this issue and the growing number of patients or animals treated with GM viral vectors.

- Concerning the **molecular characterisation of the clinical vector**, the GL-MED-GMO WG confirms the importance of providing a molecular analysis of the entire genome in order to assess its stability. This should ensure that no changes have appeared in the viral genome, particularly any that could affect the virus's biological properties. Sequencing solely at the genetic engineering site would therefore be considered insufficient. The WG also recommends in particular commenting on any changes to the viral genome (whether expected or not) that could affect the virulence of the virus, as these could lead to a change in the risk of release.
- Concerning the **biodistribution and shedding of the clinical vector**, the GL-MED-GMO WG recommends, in addition to the detection of nucleic acids from the clinical vector, searching for infectious particles to assess the risk of release. In all cases, the specificity and sensitivity of the tests used should be stated.
- The GL-MED-GMO WG confirms the need to assess the risk of **vertical transmission**.

Lastly, the GL-MED-GMO WG reiterates that measures to minimise the risks identified during the assessment should be proposed and the time frames for applying these measures should be specified.

3.3. Inclusion of the discussions held during the hearings

The draft guidelines drawn up by the GL-MED-GMO WG were discussed with the various parties consulted during a series of hearings. These hearings were then taken into account when finalising some of the recommendations set out in this opinion.

- Concerning data on the absence of **contamination of released batches by replication-competent viruses**, the hearings established that the maximum limits for replicating viral particles should be stated in the batch release specifications. Consequently, for medicinal products for human use, the GL-MED-GMO WG requests that information be provided in the ERA on detection methods and maximum contamination limits for replicating viral particles when batches are released.
- Concerning the **molecular characterisation of clinical vectors**, it emerged from these hearings that although some players or agencies do not always consider it necessary to request complete genome sequencing, this is currently easy for applicants to carry out and in some cases is already in place. Believing that its request was still justified in the context of the ERA, whether for human or veterinary medicinal products, the GL-MED-GMO WG decided to maintain this recommendation in its guidelines.
- Concerning the assessment of **stability and the sequencing of clinical vectors**, the GL-MED-GMO WG requests that the stability of the genome be analysed, by sequencing the GM virus over a number of passages appropriate to the size of the seed batches and at least equivalent to the maximum number of passages for the master seed. If a lower number is used, the applicant should justify the number of passages. The GL-MED-GMO WG agrees, as did the interviewees at the hearings, that sequencing the GM virus before batch release is unrealistic.
- Concerning the description of the **potential integration of the parental virus into the human genome**, at one of the hearings this request was deemed to be less relevant

to an assessment of the risks associated with the release of the GMO, since aspects relating to patient safety are assessed by the ANSM. The GL-MED-GMO WG nevertheless maintained this request, considering that integration into the genome could have delayed consequences in terms of release by recombination with other viral vectors or complementation, and that such a request did not raise any issue of feasibility.

- Lastly, for veterinary medicines, with regard to drawing parallels and comparing **virus distribution areas and breeding areas for target and non-target species**, one interviewee indicated that this recommendation was not feasible. The GL-MED-GMO WG considers that this is a general request, whose level of precision will depend on the data available in the literature (the applicant will not be asked to produce experimental data). The WG therefore decided to maintain this recommendation.

3.4. Conclusions of the GL-MED-GMO WG and the CES BIOTECHS

In conclusion, the GL-MED-GMO WG and the CES BIOTECHS point out that the purpose of these guidelines is to specify the information, tailored to each type of product and to current technical possibilities, required by the expert groups as part of their assessments of risks to health and the environment. The aim of this work is to ensure that each type of application for authorisation of medicinal products containing or consisting of GMOs submitted for assessment by different expert groups is processed rigorously and in a uniform manner.

The WG and the CES refer to Annexes VI to IX, which contain their guidelines and recommendations for assessing the environmental risks associated with the release of medicinal products containing GMOs.

The WG and the CES also recommend that these guidelines be regularly updated to take account of new types of GMO medicinal products that may appear on the market and potential technical developments in the assessment of these products.

Lastly, the WG and the CES recommend that similar work be carried out on the assessment of "platform technologies" (i.e. the same vector, to which a sequence of interest for medical purposes is added), for both veterinary medicinal products (for which platform certification has been possible at European level since the adoption of Commission Delegated Regulation (EU) 2021/805[3]) and medicinal products for human use, and that discussions be conducted or continued at EU level on the most critical aspects of the assessment of medicinal products containing or consisting of GMOs.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The experience acquired by ANSES since 1 January 2022, when it was entrusted with missions relating to the assessment of risks to the environment associated with the release of medicinal products containing GMOs, has highlighted the value of discussing the data expected and the most appropriate technical means of producing them, in the context of

[3] Commission Delegated Regulation (EU) 2021/805 of 8 March 2021 amending Annex II to Regulation (EU) 2019/6 of the European Parliament and of the Council In this regulation, the specific case of vaccine platforms is defined as "a collection of technologies that have in common the use of a 'backbone' carrier or vector that is modified with a different antigen or set of antigens for each vaccine derived from the platform".

marketing authorisation applications for medicinal products containing or consisting of GMOs. The purpose of the guidelines set out in this opinion is to explain these elements.

The Agency states that these guidelines will be used in its expert appraisals, when it is asked for an advisory opinion on the assessment of the risks associated with the release of medicinal products containing or consisting of GMOs. It reiterates that the results of such expert appraisals are integrated into the assessment of the medicinal product, which also takes other factors into account, such as the risk-benefit ratio associated with the need for clinical use of this medicinal product. This integration is carried out by the medicines agencies responsible for authorising these health products.

ANSES endorses the conclusions of the "GL-MED-GMO" WG and the "Biotechnologies" CES, while pointing out that these guidelines are not regulatory in nature, except where they specify an existing requirement. They constitute a guide to conducting the expert appraisal and make applicants aware of what information is recommended for better documenting and assessing the environmental risks. A footnote in the corresponding annexes explains the legal status of these guidelines.

As mentioned above, some of the experts' recommendations do not currently constitute requirements when assessing the environmental risks of GMO medicinal products. These relate to recommendations for human medicines, concerning the integration of the parental virus into the human genome, which is currently assessed solely from the perspective of patient safety, and for veterinary medicines, on the complete sequencing of the clinical vector's genome, and on drawing parallels between virus distribution areas and breeding areas for target and non-target species. Notwithstanding the absence of an explicit requirement, the Agency encourages applicants to document the corresponding information in order to increase the robustness of their risk assessments.

In issuing these guidelines designed to facilitate the expert appraisal process and the processing of dossiers, ANSES reiterates that in a centralised marketing authorisation application, the content of the modules devoted to the risks associated with the release of GMOs should be self-supporting and not refer to other parts of the dossier, and that any data on assessment of the risks associated with such release should therefore be included.

In terms of updates, ANSES supports the expert group's intention to review these guidelines periodically, in light of scientific, technical and technological advances, as well as to shed light on the accessibility and value of these elements in the examination of dossiers.

In addition, ANSES will participate in any national or European initiative designed to improve or harmonise the assessment of environmental risks associated with the release of medicinal products containing or consisting of GMOs. There are obvious needs in this area, particularly in view of the potential development of a growing number of medicines derived from biotechnologies and the issue of their direct or indirect effects on the environment, especially in gene and cell therapy.

Regarding the development of new genomic techniques, ANSES also calls for greater dialogue on these topics at both national and European levels, along the lines of the working group led by the European Commission, whose work led to the drafting of the common application forms for placing medicinal products for human use on the market. Among other

things, the Agency encourages the use of a similar approach for veterinary medicinal products to the one adopted for human medicinal products.

Pr. Benoît Vallet

KEY WORDS

Ligne directrice, risque environnemental, médicament, OGM, vétérinaire, vecteur viral, vaccin
Guideline, environmental risk, GMO, veterinary, viral vector, vaccine

SUGGESTED CITATION

ANSES. (2024). Opinion of the French Agency for Food, Environmental and Occupational Health & Safety on the development of guidelines for assessing the environmental risks associated with the deliberate release of medicinal products for human or veterinary use containing or consisting of genetically modified organisms. (Request 2022-AUTO-0167). Maisons-Alfort: ANSES, 75 p.

ANNEX I – INTERNAL REQUEST DECISION

RÉPUBLIQUE FRANÇAISE
Liberté
Égalité
Fraternité

anses

Decision No 2022-162

INTERNAL REQUEST

The Director General of the French Agency for Food, Environmental and Occupational Health & Safety (ANSES),

Having regard to the Public Health Code, and in particular its Article L.1313-3 giving ANSES the prerogative to issue an internal request on any question with a view to accomplishing its missions,

Has decided the following:

Article 1: The French Agency for Food, Environmental and Occupational Health & Safety is issuing an internal request to conduct an expert appraisal whose characteristics are listed below.

1.1 Themes and objectives of the expert appraisal

Drafting of ANSES guidelines for assessing the environmental risks associated with the deliberate release of medicinal products for human or veterinary use containing or consisting of genetically modified organisms.

1.2 Background of the internal request

On 1 January 2022, pursuant to Order No. 2021-1325 of 13 October 2021 and Decree No. 2021-1905 of 30 December 2021, ANSES took over the missions of the High Council for Biotechnology (HCB) relating to the assessment of risks to the environment and public health of all uses of biotechnologies in the open environment, whether relating to plants, animals, micro-organisms or medicinal products. These missions include environmental risk assessment (ERA) relating to the deliberate release of medicinal products for human or veterinary use containing or consisting of GMOs. As a result, ANSES can now be consulted for its opinion by:

- the DGPR, ANSM or ANMV, in connection with centralised marketing authorisation (MA) applications for medicinal products containing or consisting of GMOs under Regulation (EC) No 726/2004, Regulation (EU) No 2019/6 and Directive 2001/18/EC;
- the ANMV, in connection with applications for clinical trials to be carried out in France for veterinary medicinal products that contain or consist of GMOs, in accordance with Articles R. 533-8 and R. 533-22 of the French Environmental Code;
- the ANSM, in connection with national applications for early access authorisation (EAA) or compassionate use authorisation (CAA) for human medicinal products containing or consisting of GMOs or for authorisation of advanced therapy medicinal products prepared on an ad hoc basis, in accordance with Article R. 533-49 of the French Environmental Code.

With regard to environmental risk assessment, Articles 6 and 8 of Regulation (EC) No 726/2004 and Regulation (EU) No 2019/6, respectively, refer to Directive 2001/18/EC: "*In the case of a medicinal product for human use containing or consisting of genetically modified organisms / Where the application concerns a veterinary medicinal product containing or consisting of genetically modified organisms within the meaning of Article 2 of Directive 2001/18/EC, the application shall be accompanied by: [...] b) the complete technical dossier supplying the information required by Annexes III and IV to Directive 2001/18/EC; c) the environmental risk assessment in accordance with the principles set out in Annex II to Directive 2001/18/EC*". This describes in general terms the objective to be achieved, the information

RÉPUBLIQUE FRANÇAISE

anses

to be taken into consideration and the general principles and methodology to be followed in carrying out the environmental risk assessment referred to in Articles 4 and 13.

Guidance documents and discussion papers are available at European Union (EU) level, enabling applicants among others to identify the information needed for compiling their dossiers and complying with the ERA methodology expected by the European Medicines Agency (EMA). However, in the first dossiers processed, we identified differences in interpretation and expectations between the Member States as part of their consultation led by the EMA.

Lastly, this internal request is entirely consistent with ANSES's 2022 work programme, and particularly with the "Improving efficiency and increasing the robustness of our work" and "Initiating or completing major projects" work themes specifically identified for the Science for Expertise Division, as it could help provide a permanent and reproducible basis for environmental risk assessment. This internal request could also contribute to the work planned in Sheet 1.3.2 "METHEVALOGM" of the Science for Expertise Division's 2021 work programme. Before the HCB's missions were transferred to ANSES, this programme included in-depth work on risk assessment methods specific to the use of GMOs in feed and food.

1.3 Questions on which the expert appraisal work will focus

Based mainly on the guidance documents and discussion papers available at national level or within the European Union, the opinions and comments previously issued by the HCB or ANSES, as well as by the other Member States, and the opinions and comments formulated by EMA, the work carried out as part of this internal request will aim to **draw up ERA grids for assessing each type of dossier (MA application, clinical trial, specific authorisation) on the deliberate release of medicinal products for human or veterinary use containing or consisting of GMOs, paying particular attention to the analysis methods expected in support of the ERA. Guidelines will be proposed on the basis of these assessment grids.**

1.4 Estimated duration of the expert appraisal

The expert appraisal is estimated to take 12 months.

Article 2: An opinion will be issued and published by the Agency following completion of the work.

Signed at Maisons-Alfort, on 26 September 2022.

Dr Roger GENET
Director General

ANNEX II – LIST OF PARTICIPANTS

PREAMBLE: The expert members of the Expert Committees and Working Groups or designated rapporteurs are all appointed in a personal capacity, *intuitu personae*, and do not represent their parent organisation.

WORKING GROUP (WG)

- "GL-MED-GMO" WG (2022-2024)

Chair

Ms Marie-Bérengère TROADEC – Professor – University of Brest – Genetics, oncology

Members

Mr Florian GUILLOU – Research Director – INRAE – Physiology of human reproduction, animal production

Mr Bernard KLONJKOWSKI – Researcher – Alfort National Veterinary School – Virology, molecular characterisation

Mr François MOREAU-GAUDRY – University Professor – Hospital Practitioner, Team Leader (University of Bordeaux) – Genome editing techniques, gene therapy

EXPERT COMMITTEE (CES)

The work that is the subject of this report was monitored and adopted by the following Expert Committee:

- CES on "Biotechnologies" (2024-2028) – 11 March 2024 and 9 April 2024

Chair

Ms Laurence VERNIS – Research Officer – Inserm – Genetics and physiology of micro-organisms, molecular biology, redox biology

Vice-Chairs

Mr Florian GUILLOU – Research Director – INRAE – Physiology of human reproduction, animal production

Ms Marie-Bérengère TROADEC – Professor – University of Brest – Genetics, oncology

Members

Ms Elisabeth BAEZA – Research Engineer – INRAE – Animal nutrition, feed composition, poultry husbandry

Mr Luc BELZUNCES – Research Director – INRAE – Toxicology and ecotoxicology – Physiology, cellular and molecular biology, metabolism – Analytical chemistry – Risk assessment

Mr Christophe BOËTE – Research Officer – IRD – Evolutionary ecology, medical entomology, vector control

Mr Rémy CACHON – University Professor – Institut Agro Dijon – Biotechnological process engineering, microbiology, enzymology

Ms Marie-Christine CHAGNON – University Professor – Institut Agro Dijon – Food toxicology, chemical contaminants, risk assessment

Mr Nicolas DESNEUX – Research Director – INRAE – Environmental toxicology, invasive species, crops and ecosystems

Mr Olivier FIRMESSE – Research Project Leader – ANSES – Microbial ecology, food pathogens, molecular biology, *Bacillus thuringiensis*

Mr Michel GAUTIER – Professor – Institut Agro Rennes-Angers – Microbiology including food microbiology (fermented foods and food safety), genetic engineering, bacteriophages

Mr Philippe GUERCHE – Research Director – INRAE – Plant transgenesis, molecular characterisation, genetics

Ms Claire HELLIO – Professor – University of Western Brittany – Marine biotechnologies (enzymology, environmental microbiology, biologically active natural marine products)

Ms Nolwenn HYMERY – Lecturer – University of Western Brittany – Food toxicology

Mr Bernard KLONJKOWSKI – Researcher – Alfort National Veterinary School – Virology, molecular characterisation

Ms Valérie LE CORRE – Research Officer – INRAE – Population genetics, agronomy, evolutionary ecology, weeds and invasive plants

Mr Matteo LENER – Research Officer – Italian Institute for Environmental Protection and Research (ISPRA) – Environmental risk assessment, genetic engineering

Mr David MAKOWSKI – Research Director, INRAE – Statistical analysis, modelling, meta-analysis, agronomy

Ms Julie MALLET – Research Project Leader – ANSES – Molecular biology, GMO detection methods, plant physiology

Ms Marianne MAZIER – Research Engineer – INRAE – Genetic engineering, plant transgenesis, plant improvement

Mr François MEURENS – Professor – University of Montreal – Veterinary immunology (host/pathogen relationships, innate immunity, mucosal immunology, veterinary vaccines), virology, *Chlamydia* sp. and biomedical models (pigs)

Mr Sergio OCHATT – Retired Researcher – INRAE – Plant physiology, genetics, transgenesis

Mr Pierre ROUGE – Professor Emeritus – Toulouse III University – Allergology

Ms Patricia TAILLANDIER – Professor – INP ENSIACET – Technological fermentation processes, enzymology, microbiology, biochemistry

Ms Corinne TEYSSIER – Lecturer – University of Montpellier – Food microbiology, microbial ecology, food security

ANSES PARTICIPATION

Scientific coordination

Mr Dylan CHERRIER – Scientific Expert Appraisal Coordinator for the Biotechnologies Unit – Risk Assessment Department (DER) – ANSES

Ms Lucie EYRAUD – Scientific Expert Appraisal Coordinator for the Biotechnologies Unit – DER – ANSES

Mr Youssef EL OUADRHIRI – Head of the Biotechnologies Unit – DER – ANSES

Administrative secretariat

Ms Armelle VIGNERON – Expert Appraisal Support Department – DER – ANSES

HEARINGS

French Agency for Veterinary Medicinal Products (ANMV – ANSES)

Ms Christine MIRAS – MA Dossier Rapporteur, alternate member for France on the CVMP

Mr Jean-Claude ROUBY – Scientific Advisor for immunology and new therapies

National Agency for Medicines and Health Products Safety (ANSM)

Representative of the ANSM, responsible for advanced therapy medicinal products

Expert Committee on contained uses of GMOs (CEUCO)

Mr Jean-Christophe PAGÈS – Chair

French Union for the Veterinary Medicinal Product and Diagnosis Industry (SIMV)

Mr Frédéric REYNARD – Project Manager at Boehringer Ingelheim Animal Health, SIMV representative on ANSES's "Biotechnology, Environment and Health" dialogue committee.

Transgene

Mr Éric QUÉMÉNEUR – Scientific Director

Mr Julien ROMANETTO – Regulatory Affairs Officer

ANNEX III – BODY OF LITERATURE

Title and creation date	Content	Applicability	Interest with respect to the topic, according to the WG	Justification
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 (Version of 20 June 2019) https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32001L0018	Main text establishing the assessment procedure in the event of the deliberate release of GMOs. In particular, Annex II defines the content of the ERA, and Annex IIIA the content of the technical dossier	Any deliberate release	**Important**	Main European regulatory text on GMOs. Contains, in particular, a description of the information required for the technical dossier and the ERA
Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) 726/2004 (Version of 20 June 2019) https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32007R1394	Text specifying the MA procedure for advanced therapy products, establishing the Committee for Advanced Therapies. Refers to Regulation (EC) No 726-2004	MA for an advanced therapy medicinal product for human use	Low	Procedural clarification, but no additional information on what is expected from the dossier
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 (Version of 11 December 2018) https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32004R0726	Text specifying the MA procedure for medicinal products for human use and establishing EMA. Refers to Directive 2001/18/EC	MA for a medicinal product for human use	Low	Procedural clarification, but no additional information on what is expected from the dossier

Title and creation date	Content	Applicability	Interest with respect to the topic, according to the WG	Justification
Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC (Version of 27 February 2023) https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32019R0006	Text specifying the MA procedure for veterinary medicinal products. Refers to Directive 2001/18/EC	MA for a veterinary medicinal product	Low	Procedural clarification, but no additional information on what is expected from the dossier
Ministerial Order of 16 December 2019 laying down the contents of the technical dossier accompanying the application for authorisation for deliberate release of GMOs in the context of clinical trials for veterinary medicinal products https://www.legifrance.gouv.fr/jorf/id/JORFTEXT000039630748	Text setting out the content of the technical dossier to be provided in the context of a veterinary clinical trial (content identical to Annex IIIA of Directive 2001/18/EC)	Veterinary clinical trial	**Moderate**	Regulatory text establishing the technical dossier for a clinical trial. Moderate interest, as identical to Directive 2001/18/EC
Ministerial Order of 25 January 2022 on the technical dossier required for the contained use of GMOs provided for in Articles R. 532-6, R. 532-14 and R. 532-26, and the risk assessment dossier provided for in Article L. 532-3 of the Environmental Code https://www.legifrance.gouv.fr/jorf/id/JORFTEXT000045084588	Text setting out the content of the technical dossier to be provided for an application for the contained use of a GMO medicinal product (separation of viral vectors, AAV, GM cells)	Contained use	Low	Regulatory text establishing the use of common application forms (CAFs) for clinical trials conducted in France. Low interest; falls outside the area of competence
French Environmental code – Chapter III: Deliberate release and placing on the market of genetically modified organisms (Articles R533-1 to R533-51) (Version of 30 December 2021) https://www.legifrance.gouv.fr/codes/section_lc/LEGITEXT000006074220/LEGISCTA000006159428/	Text setting out ANSES's powers in terms of assessing the environmental risks of GMO medicinal products	Any deliberate release	Low	Procedural clarification, but no additional information on what is expected from the dossier

Title and creation date	Content	Applicability	Interest with respect to the topic, according to the WG	Justification
Guideline on the environmental risk assessment of medicinal products for human use (Version of 1 June 2006) https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-environmental-risk-assessment-medicinal-products-human-use-revision-1_en.pdf	Guideline for conducting an ERA of medicinal products for human use. Does not concern the scope assessed by ANSES, provided for information only	MA for a medicinal product for human use	Low	Outside area of competence
Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products (Version of 30 May 2008) https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-scientific-requirements-environmental-risk-assessment-gene-therapy-medicinal-products_en.pdf	Specific guideline for an ERA of gene therapy medicinal products for human use	MA for a gene therapy medicinal product for human use	**Important**	Sets out the expectations of the ERA
Guideline on environmental risk assessments for medicinal products consisting of, or containing, genetically modified organisms (GMOs) (Version of 11 December 2006) https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-environmental-risk-assessments-medicinal-products-consisting-or-containing-genetically-modified-organisms-gmos_en.pdf	General guideline for an ERA of GMO medicinal products for human use (does not contain details on what is expected in the technical dossier)	MA for a medicinal product for human use	**Important**	Sets out the expectations of the ERA
Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (Version of 12 November 2020) https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-and-clinical-aspects-medicinal-products-containing-genetically-modified-cells-revision-1_en.pdf	Guideline for the general assessment of genetically modified cells – document covers a broader scope than that assessed by ANSES (see the section devoted to the ERA, the other sections may specify certain technical expectations)	MA for a medicinal product containing GM cells for human use	**Moderate**	Clarification of technical expectations outside the field of expertise but that may have an impact on the ERA

Title and creation date	Content	Applicability	Interest with respect to the topic, according to the WG	Justification
Guideline on quality, non-clinical and clinical aspects of live recombinant viral vectored vaccines (Version of 24 June 2010) https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-and-clinical-aspects-live-recombinant-viral-vectored-vaccines_en.pdf	Guideline for the general assessment of recombinant viral vectors – document covers a broader scope than that assessed by ANSES (which may specify certain technical expectations)	MA for a live recombinant vaccine for human use	**Moderate**	Clarification of technical expectations outside the field of expertise but that may have an impact on the ERA
European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure (Version of 21 December 2022) https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-pre-authorisation-procedural-advice-users-centralised-procedure_en.pdf	Notice to applicants, specifying that in the case of medicinal products for human use containing AAVs, viral vectors or GM cells, the technical dossier stipulated by Directive 2001/18/EC may be replaced by the corresponding CAFs (Section 3.4.3)	MA for a medicinal product for human use	**Important**	Regulatory text setting out the use of CAFs for MA applications
Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use' (Version of 26 May 2016) https://www.ema.europa.eu/en/documents/scientific-guideline/questions-and-answers-guideline-environmental-risk-assessment-medicinal-products-human-use-revision-1_en.pdf	FAQ on the guideline for conducting an ERA of medicinal products for human use. Does not concern the scope assessed by ANSES, provided for information only	MA for a medicinal product for human use	Low	Outside area of competence
Questions and answers on gene therapy (Version of 17 December 2009) https://www.ema.europa.eu/en/documents/scientific-guideline/questions-and-answers-gene-therapy_en.pdf	FAQ on gene therapy medicinal products for human use (for information)	MA for a gene therapy medicinal product for human use	Low	Outside area of competence

Title and creation date	Content	Applicability	Interest with respect to the topic, according to the WG	Justification
Guideline on the definition of a potential serious risk to human or animal health or for the environment in the context of Article 33(1) and (2) of Directive 2001/82/EC (Version of March 2006) https://health.ec.europa.eu/document/download/d82307d2-cb4d-4504-aef5-147a1ac08db5_en?filename=2006_c_132_08_en.pdf	Definition of a "serious risk" to the environment as mentioned in Directive 2001/82/EC (repealed by Regulation (EU) No 2019/6)	MA for a veterinary medicinal product	Low	Document relating to a repealed text
Guidance on the assessment of environmental risks of veterinary medicinal products (Version of 24 June 2009) https://health.ec.europa.eu/document/download/6a365da6-f5fe-4d93-96f7-fdf2951d5f53_en?filename=2009-03-17_era-cvmp_nta_en.pdf	Guideline for conducting an ERA of veterinary medicinal products. Does not concern the scope assessed by ANSES, provided for information only	MA for a veterinary medicinal product	Low	Outside area of competence
Guidance on environmental risk assessment for veterinary medicinal products consisting of or containing genetically modified organisms (GMOs) (Version of March 2017) https://health.ec.europa.eu/document/download/e9e4980a-6fb3-44ee-be73-9b00c1c43c7d_en?filename=vol6c_gmo_guidance_2017_03.pdf	General guideline for an ERA of GMO veterinary medicinal products (does not contain details on what is expected in the technical dossier)	MA for a veterinary medicinal product	**Moderate**	Sets out the expectations of the ERA, but has not yet been updated following recent regulatory changes
Note for guidance: environmental risk assessment for immunological veterinary medicinal products (Version of 24 July 1996) https://www.ema.europa.eu/en/documents/scientific-guideline/note-guidance-environmental-risk-assessment-immunological-veterinary-medicinal-products_en.pdf	Guideline for an ERA of immunological veterinary medicinal products (does not contain details on what is expected in the technical dossier)	MA for a veterinary medicinal product	**Moderate**	Sets out the expectations of the ERA, but has not yet been updated following recent regulatory changes

Title and creation date	Content	Applicability	Interest with respect to the topic, according to the WG	Justification
Guideline on good clinical practices (Version of 4 July 2020) https://www.ema.europa.eu/en/documents/scientific-guideline/vich-gl9-good-clinical-practices-step-7_en.pdf	General guideline for conducting veterinary clinical trials	Veterinary clinical trial	Low	Outside area of competence
Common application form for investigational medicinal products for human use that contain or consist of AAV vectors (Version of October 2019) https://health.ec.europa.eu/system/files/2022-01/aavs_caf_en.pdf	CAF for the contained use of medicinal products for human use containing an AAV vector (also applicable to MA applications)	Contained use and placing on the market of a medicinal product containing an AAV vector for human use	**Important**	Contains a description of the information needed for an MA application for the type of medicinal product in question
Good Practice on the assessment of GMO related aspects in the context of clinical trials with AAV clinical vectors (Version of October 2019) https://health.ec.europa.eu/document/download/62bc65ee-7f74-4b76-bdc3-07909ab177ee_en?filename=aavs_gp_en.pdf	Guideline specific to the ERA of medicinal products for human use containing an AAV vector for contained use (also applicable to MA applications)	Contained use and placing on the market of a medicinal product containing an AAV vector for human use	**Important**	Sets out the expectations of the ERA of the type of medicinal product concerned
Common Application form for clinical research with human cells genetically modified (Version of July 2018) https://health.ec.europa.eu/system/files/2021-11/gmcells_caf_en_0.pdf	CAF for the contained use of medicinal products for human use containing GM cells (also applicable to MA applications)	Contained use and placing on the market of a medicinal product containing GM cells for human use	**Important**	Contains a description of the information needed for an MA application for the type of medicinal product in question

Title and creation date	Content	Applicability	Interest with respect to the topic, according to the WG	Justification
Good Practice on the assessment of GMO-related aspects in the context of clinical trials with human cells genetically modified (Version of July 2018) https://health.ec.europa.eu/document/download/01b23303-0d60-40ae-81a6-3ef52a4468f5_en	Guideline specific to the ERA of medicinal products for human use containing GM cells for contained use (also applicable to MA applications)	Contained use and placing on the market of a medicinal product containing GM cells for human use	**Important**	Sets out the expectations of the ERA of the type of medicinal product concerned
Oncolytic viruses: considerations for the evaluation of shedding (Version of December 2020) https://health.ec.europa.eu/system/files/2022-01/oncolytic_evaluation_en.pdf	Considerations on the shedding of oncolytic viruses	Contained use of a medicinal product containing oncolytic viruses for human use	**Important**	A discussion paper on an important aspect of the risk of release
Medicinal products for human use containing or consisting of GMOs: interplay between the EU legislation on medicinal products and GMOs (Version of July 2018) https://health.ec.europa.eu/system/files/2019-10/gmcells_qa_en_0.pdf	FAQ on procedures relating to the assessment of GMO medicinal products for contained use	Contained use and placing on the market of a medicinal product for human use	Low	Outside area of competence
Common application form for viral vectors contained in investigational medicinal products for human use (Version of October 2019) https://health.ec.europa.eu/system/files/2022-01/vvs_caf_en.pdf	CAF for the contained use of medicinal products for human use containing viral vectors other than AAVs (also applicable to MA applications)	Contained use and placing on the market of a medicinal product containing a viral vector for human use	**Important**	Contains a description of the information needed for an MA application for the type of medicinal product in question

ANNEX IV – FRAMEWORKS AND MINUTES OF VALID HEARINGS

1. Hearings of 9 January 2023

1.1 Framework of the hearing

Objective 1: Ensure that the documents identified by the WG are exhaustive – regulatory documents and national (France and abroad) or EU reference documents, internal resources, technical documents.

Objective 2: Understand the scope and reach of the various documents identified, in particular the common application forms for advanced therapy medicinal products.

Objective 3: Understand the assessment methodology and reference documents used in the context of contained uses.

Objective 4: Understand the specific features and requirements of veterinary clinical trials.

Objective 5: Understand the specific features and requirements of early access authorisations (EAAs) and compassionate access authorisations (CAAs) – assessment history, content of the dossier to be examined, reference documents.

Objective 6: Ensure that the correct level of assessment is carried out, according to the specific cases associated with the type of medicinal product (AAV vector, GM cells, other cases, etc.).

Miscellaneous questions: Prospects for placing products on the market, possible changes to regulations, other players to be interviewed.

1.2 Hearing with the representative of the ANSM responsible for advanced therapy medicinal products

By way of introduction, regarding the reference documents for assessing the environmental risks associated with medicinal products containing GMOs, the ANSM representative indicated that following major efforts to achieve consensus, a working group set up by the European Commission to harmonise the practices of the various Member States in assessing applications to authorise GMOs for clinical trials of advanced therapy medicinal products (in anticipation of regulatory changes concerning the introduction of a centralised procedure for clinical trial authorisation applications in Europe) led to common application forms (CAFs)[4] and best practice documents being drawn up for each type of medicinal product (GM cells, GM AAVs, GM viral vectors other than AAVs), which were then adopted by the Member States on a voluntary basis. In France, the use of CAFs for clinical trial authorisation applications has been set out in a ministerial order[5]. CAFs can also be used for centralised MA applications. To date, all advanced therapy medicinal products that have been granted marketing authorisation have been assessed as presenting a negligible risk to the environment.

[4] The CAFs and best practice documents are available at https://health.ec.europa.eu/medicinal-products/advanced-therapies_en
[5] Ministerial Order of 25 January 2022 on the technical dossier required for the contained use of genetically modified organisms provided for in Articles R. 532-6, R. 532-14 and R. 532-26, and the risk assessment dossier provided for in Article L. 532-3 of the Environmental Code

The ANSM representative was then questioned by Ms TROADEC on the exhaustiveness of the list of regulatory documents and guidance documents available at national or European level, presented by the working group. It was pointed out that the *Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products* (EMEA/CHMP/GTWP/125491/2006) and *Guideline on environmental risk assessments for medicinal products consisting of, or containing, genetically modified organisms (GMOs)* (EMEA/CHMP/BWP/473191/2006 – Corr) are old, and have not been updated since the Member States' voluntary adoption of the CAFs. It was stated on the other hand that the *European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure* (EMA/821278/2015) was updated in December 2022, with a view to clarifying the use of CAFs in the context of a centralised MA. Lastly, it was reminded that the good practice documents[1] specify the conditions to be fulfilled to allow the use of a CAF, and that the document *Medicinal products for human use containing or consisting of GMOs: interplay between the EU legislation on medicinal products and GMOs* defines the products to be assessed as medicinal products containing GMOs, and contains a specific form for clinical trial authorisation applications for medicinal products that already have marketing authorisation (outside the scope of this internal request).

In response to a question about the ANSM's processing of clinical trial authorisation applications, the ANSM representative explained that, prior to the transfer of this mission from the French Ministry of Higher Education, Research and Innovation to the ANSM in June 2022, a questionnaire for sponsors had been drawn up with the Scientific Committee of the High Council for Biotechnology to enable rapid differentiation of applications to be forwarded to the Expert Committee on contained uses of GMOs (CEUCO) for an opinion. It was agreed that this questionnaire would be forwarded to the working group. Because the questionnaire included a question on the containment level associated with the medicinal product, Mr KLONJKOWSKI reiterated that AAV vectors must be produced with a C2 containment level, but that a C1 containment level is sufficient for their use. The ANSM representative replied that production of the medicinal product is not assessed, and that any variations in containment levels between Member States are not necessarily a problem insofar as the assessment focuses on the risks of release during and after administration of the product.

Concerning applications for early access authorisation (EAA) or compassionate access authorisation (CAA), the ANSM will ask the applicant to provide a CAF (in the absence of a prior assessment of the risk associated with the deliberate release of the GMO), which it will forward to ANSES for assessment, with similar requirements to those for a marketing authorisation application. The response time is laid down by the regulations[6], but emergency situations may arise (particularly for CAAs), which would require a faster response from ANSES.

In response to a question from Mr MOREAU-GAUDRY, it was stated that dossiers on genetically modified oncolytic viral vectors had indeed been received this year in connection with clinical trial authorisation applications. It was also specified that for integrating viral

[6] Post-session note from coordination: Article R. 533-29 of the Environmental Code stipulates a period of 60 days from the date on which the application is registered by ANSES – this period is also valid for applications for advanced therapy medicinal product prepared on an ad hoc basis (MTI-PP).

vectors, such as lentiviral and retroviral vectors, patient follow-up is planned over a period of 15 years, and that a similar period is now required for medicinal products containing a genetically modified AAV when obtaining European MA. Looking ahead, the ANSM representative indicated that bacteriophages or recombinant bacteria could be assessed in the future. It was also stated that the European directives on medicinal products will be revised in the medium term, and could amend the regulations on medicinal products containing GMOs.

1.3 Hearing with Mr Jean-Christophe PAGÈS (Chair of the CEUCO)

By way of introduction, Mr PAGÈS stated that he had been Chair of the High Council for Biotechnology and of its Scientific Committee, and was now Chair of the Expert Committee on contained uses of GMOs, and that he had participated in the European working group that led to the CAFs being drawn up.

Mr PAGÈS began by clarifying that Directive 2001/18/EC considers any marketing authorisation to be a release, but emphasised that in the context of the assessment of medicinal products containing GMOs, the assessors focus on analysing the risks associated with a "biological release". In the case of medicines for human use, these risks are also assessed as part of clinical trials, and to date have always been deemed negligible. The two meanings therefore need to be clearly distinguished. In response to a question from Ms TROADEC, Mr PAGÈS clarified that "vertical" release was also taken into account, adding that it seemed unlikely, with the possible exception of non-enveloped vectors that could be found in seminal fluids. Mr PAGÈS added that the issue of shedding could lead to the reference documents being modified, as genetic material has been found in biological fluids following the administration of gene therapy medicinal products, albeit without any link with transfer capability having been demonstrated to date; knowledge on this subject continues to evolve (particularly in terms of the transmissibility of this material to directly exposed individuals). He nevertheless pointed out that there is currently no relevant test that can satisfactorily verify this characteristic, and that in his opinion the CAFs satisfactorily cover the various known risks for the viral vectors currently in use.

In response to a question from Ms TROADEC, Mr PAGÈS indicated that in the absence of details on some of the CAF sections, the level of precision provided by applicants was not always satisfactory, leading to back-and-forth exchanges with the assessors in order to obtain all the data required for the analysis. Specifically concerning the sequencing of viral strains, Mr PAGÈS agreed that in the case of oncolytic viruses, it was reasonable to ask for the complete vector sequence to be provided, and for producers to specify the various checks carried out before batches are released to confirm the absence of genetic drift in relation to the theoretical sequence.

Looking ahead, Mr PAGÈS indicated that for any future medicinal products based on CRISPR-Cas technology, he did not envisage any additional risks to the environment, and that the risks associated with any undesirable effects, whether at the target site or not, would be outside the scope of the environmental risk assessment but would be taken into account by the ANSM. He also indicated that recombination systems based on transposons could be assessed in the future. Concerning possible changes to the regulations, Mr PAGÈS would consider a "tiered"

assessment, tailored to each type of medicinal product on the basis of known risks and pragmatic on the basis of the known data, pharmacovigilance and the technical possibilities available to date. In response to a question from Mr KLONJKOWSKI, Mr PAGÈS stated that although there was no body bringing together the ANSM, ANSES and the CEUCO, he did not see any weaknesses in the current procedures for assessing medicinal products containing GMOs.

1.4 Hearing with Ms Christine MIRAS (MA Dossier Rapporteur at the ANMV and alternate member for France on the CVMP)

By way of introduction, Ms MIRAS stated that she was the alternate member for France on EMA's Committee for veterinary medicinal products (CVMP).

Ms MIRAS then explained that the list of regulatory and guidance documents previously presented by the working group could be supplemented with *VICH Topic GL9 – Guideline on good clinical practices* (CVMP/VICH/595/98-FINAL), which defines good practices for veterinary clinical trials, and *Note for guidance: environmental risk assessment for immunological veterinary medicinal products* (EMEA/CVMP/074/95), a document specific to immunological medicinal products. Ms MIRAS also pointed out that the *Notice for applicants (Guidance on environmental risk assessment for veterinary medicinal products consisting of or containing genetically modified organisms)* referred to texts that have now been repealed, and that a new version was being drafted and should be available in June 2023. Lastly, Ms MIRAS stated that, to her knowledge, there was no document specifying the technical details (in terms of the technologies used, for example) expected in the dossier provided by the applicant, beyond the framework set by Directive 2001/18/EC, and that the CVMP made every effort to verify whether the genetic modification leads to a change in the properties of the parental strain. In this respect, it should be noted that for each new formal request, the ANMV will inform the Risk Assessment Department of prior authorisations for the strain in question.

In response to a question from Ms TROADEC about the specific features of veterinary clinical trial authorisations, Ms MIRAS indicated that the dossiers were processed by other people in her department, within the ANMV. It was therefore agreed that contact could be made after the hearing with the staff members concerned, if any questions on clinical trials arose during preparation of the assessment grids.

Looking ahead, Ms MIRAS pointed out that innovative medicinal product technologies initially developed for human medicine could potentially appear in veterinary medicine in the medium term, but that the development of these new medicinal products was limited by research and development costs. In response to a question from Mr KLONJKOWSKI, Ms MIRAS stated that new recombinant vaccines may also emerge for domestic carnivores and horses, with some vaccines already available on the market.

2. Hearings of 28 and 29 June 2023

2.1 Framework of the hearing

Objective 1: Discuss the relevance of the proposed guidelines in the context of risk assessment.

Objective 2: Discuss the technical feasibility of the proposed guidelines.

Objective 3: Compare the proposed guidelines with European expectations.

Objective 4: Discuss any adaptations that may be necessary in the context of clinical trials.

Miscellaneous questions:

Prospects for placing products on the market and changes in the type of products submitted for authorisation.

Future developments in analysis methods for medicinal products.

Possible changes to regulations.

2.1 Hearing with the representative of the ANSM responsible for advanced therapy medicinal products

The ANSM representative reminded those present of the structure of marketing authorisation applications for medicinal products for human use. The dossier is divided into five modules: an initial administrative module (containing in particular the ERA), a second module with summaries of the three following modules, and then three modules devoted, respectively, to quality, non-clinical studies and clinical studies (without individual data). The quality module contains batch release specifications, including a maximum detection threshold for replicating viral particles. Guidelines also clarify what is expected in terms of the batch release specifications.

Concerning vector stability, the ANSM representative indicated that, from a pharmaceutical perspective, this was mainly determined according to functional criteria, and questioned the relevance of complete sequencing, insofar as, for example, it would not be possible to rule out mutations in the viral vector once it had been administered. The WG experts explained that the request related more to the production stages: firstly to ensure the intrinsic stability of the vector used, and secondly to check that the production stages are adequately controlled and do not lead to genomic instability. The ANSM representative indicated that it would be beneficial for these points to be discussed with the other European GMO assessment agencies. Mr CHERRIER stated that discussions with the other European agencies could be initiated after the opinion is finalised, once the French position has been established.

The ANSM representative informed the WG that the European Commission is currently revising the pharmaceutical directives, and is considering centralising applications for authorisation to use medicinal products containing GMOs in clinical trials at the level of EMA's Committee for Medicinal Products for Human Use (CHMP), which would be supported by a working party whose composition has not yet been detailed (discussions are not yet under way at this stage). This working party could be a forum for dialogue on expectations regarding

medicinal product assessment, but would only come into being in the medium term if this option is decided on.

Concerning shedding, the ANSM representative indicated that the assessment was based on pre-clinical data on biodistribution in animals and on clinical data from fluids collected, and specified that the data obtained by PCR do not generally provide information on the infectivity of the viral vector. The ANSM representative added, however, that a dossier presenting a PCR able to distinguish infectious viral particles from non-infectious ones had already been examined, and pointed out that shedding is also assessed by the medicines agencies, and that suitable contraception methods are systematically called for in the event of GMOs being detected in semen.

Concerning gene therapies consisting of genetically modified cells, and in particular the potential off-target effects due to the modification techniques used in the genome of the cells making up the medicinal product, the ANSM representative explained that in the case of CAR-T cells, the secondary lymphomas observed were not attributed to the gene therapy, but rather to the treatments received prior to administration of the medicinal product. As far as they knew, the observation of potential off-target effects or natural mutations in the lymphoid lineage affecting the risk of vertical transmission had never been described.

2.2 Hearing with Mr Jean-Christophe PAGÈS (Chair of the CEUCO)

By way of introduction, Mr PAGÈS stated that he had been Chair of the High Council for Biotechnology (HCB) and of its Scientific Committee until December 2021, and that in this capacity he had participated in the European working group that led to the common application forms (CAFs) being drawn up. He has been Chair of the Expert Committee on contained uses of GMOs (CEUCO) since its creation in 2022.

Mr PAGÈS began by stating that the conditional nature of replicating viral vectors was central to the assessment, as the probability of a medicinal product containing an "absolute" replicating GMO was low. He indicated that data on attenuation of the replicative properties of these viral vectors (literature or experimental demonstration) should be readily available from applicants. Regarding the characteristics of the parental virus, Mr PAGÈS pointed out that when assessing the risk of the GMO being released into the environment, the steps to integrate the viral vector should only be taken into account if they can take place in the germ line. Mr KLONJKOWSKI explained that the WG wanted this information to be provided in order to better understand the potential consequences of contact between a person (other than a treated patient) and the GMO, for example in the case of healthcare professionals or release into the patient's immediate environment. Mr PAGÈS pointed out that while this was an interesting question, it did not seem to be a priority in terms of assessing the risk of release of the GMO into the environment. He suggested rewording the associated guideline and simplifying part of it by asking for the Investigational Medicinal Product Dossier to be supplied.

Concerning the request for analysis of the complete sequencing of viral vectors, Mr PAGÈS believed that these data were also available from applicants and it should therefore be possible to provide them. Mr PAGÈS considered that the question of verifying the stability of the

sequence could nevertheless arise, and in particular the steps at which verification should be carried out (seeding, batch release, etc.). He believed that while these data were generally available for the initial production phases, they would not necessarily be available for the release of batches (which would nevertheless be checked for their biological activity), and that it may be worthwhile in this case to ask for other information than sequencing to be provided, which would help ensure the stability of the sequence.

Concerning information on biodistribution and shedding, Mr PAGÈS agreed with the WG's requests relating to the provision of all available experimental data (particularly particle infectivity data and clinical data). Mr PAGÈS also agreed with the WG's request for the applicant to analyse the environmental risks (in the broader sense, Section 5.6 of the CAF) associated with the GMO medicinal product.

In response to a question from Mr KLONJKOWSKI about risk management measures, Mr PAGÈS stated that the measures planned by the applicant were detailed in the patient information leaflet, and that the applicant could be asked to supplement them depending on the data on shedding (neutralisation of urine before elimination, wearing a mask, wiping away tears, etc.).

Concerning genetically modified cells, Mr PAGÈS believed that the issue of modifying their persistence had little impact on the assessment of release into the environment, as the main risks associated with these possible modifications concerned the safety of the medicinal product for the patient and were therefore taken into account elsewhere (survival of the cell outside the treated patient being extremely unlikely). Mr PAGÈS also indicated that regardless of which transformation tool was used, any transformation detected should be accompanied by an argument as to whether or not it is transferable, as this point can be difficult to assess experimentally.

2.3 Hearing with Mr Jean-Claude ROUBY (Scientific advisor for immunology and new therapies at the ANMV)

By way of introduction, Mr ROUBY stated that he was the Scientific Advisor for Immunology and New Therapies at ANSES/ANMV.

Concerning the request to draw parallels between the breeding areas for target and non-target species and the geographical distribution of the parental organism, Mr ROUBY considered that applicants would have a great deal of work to do, as data on the distribution of the different strains were not always known and would not make a significant contribution to assessing the risk of GMO release. Mr ROUBY pointed out that with a vaccine, the studies requested elsewhere in the authorisation dossier would be sufficient to assess the environmental risks of the GMO, particularly relating to recombination. It was also specified that when a vaccine, GMO or not, can induce a reaction in a species for which it is not intended, studies are required under the regulations and may lead to the medicinal product not being authorised. Lastly, Mr ROUBY explained that sector-based authorisations within the EU are not possible. Indications or contraindications for species can be indicated in the medicinal product's summary of product

characteristics (SPC), but the use of the medicinal product remains the responsibility of the veterinarian, who can administer medicinal products "off label".

Mr ROUBY then explained that, with a few rare exceptions, veterinary medicinal products containing GMOs are based on platform technologies, which applicants can now register with EMA (since Regulation (EU) 2019/6). Registration of the platform technology enables it to be assessed at the time of submission, in parallel with the assessment of a medicinal product containing it, and then to be authorised for use without further assessment for future medicinal products (in which case only the insert is assessed).

Concerning the complete sequencing of vectors, Mr ROUBY indicated that he did not think this request would be useful, and that it was unlikely that the CVMP would agree to it. He also pointed out that complete sequencing of the genome would generate data that would be difficult to interpret. Ms TROADEC and Mr KLONJKOWSKI stressed the importance for the WG of being able to ensure that the addition of the insert had not led to any changes in the rest of the genome, particularly in genes linked to the vector's tropism and virulence. Mr ROUBY pointed out that in veterinary medicine, there is currently only one clonal vaccine. He indicated that he considered safety studies to be sufficient to ensure the vaccine's stability before it is placed on the market, and that this regulatory "constraint" could have an impact on the authorisation applications (the more stringent the requirements, the fewer applications there are). Lastly, Mr ROUBY pointed out that, on the other hand, a greater effort could be made by the public services to ensure the stability of vaccine strains when the vaccines containing them have been authorised for a long time.

In the case of multivalent vaccines, Mr ROUBY explained that the legislation requires specific safety studies to be performed on potential recombinations between strains. Similarly, specific management measures for waste that may contain the shed GMO are not generally required, insofar as the safety of the GMO is deemed to have been demonstrated.

2.4 Hearing with Mr Frédéric REYNARD (Project Manager at Boehringer Ingelheim Animal Health and SIMV representative)

By way of introduction, Mr REYNARD stated that he was Project Manager at Boehringer Ingelheim Animal Health and a representative of the French Union for the Veterinary Medicinal Product and Diagnosis Industry (SIMV). In this capacity, he is a member of ANSES's "Biotechnology, Environment and Health" dialogue committee.

Concerning the WG's proposal to request parallel information on the breeding areas of the medicinal product's target and non-target species and the geographical distribution of the parental virus, Mr REYNARD indicated that he felt it was relevant to the assessment of the interaction between the GMO and its ecosystem, but that he could not comment on its feasibility, which would depend on the level of detail required and could vary depending on the organism in question. He also stated that, in general, he was in favour of regulatory changes that would take better account of the specific features of medicinal products containing GMOs, as current legislation is more suited to genetically modified plants. In response to a question from Mr KLONJKOWSKI, Mr REYNARD stated that the capacity for horizontal transmission, pathogenicity to non-target species and recombination potential of GMO medicinal products

were central elements in the assessment of medicinal products containing GMOs, but that the existence of a risk of horizontal transmission to a non-target species without a pathogenic effect on this species should not necessarily be a barrier to their authorisation.

In order to assess the recombination potential of medicines containing GMOs, Mr REYNARD indicated that, in general, industry players primarily sought to understand whether recombination could produce a new virus that was more virulent or had a different tropism to that of the pathogenic strain, since the recombination potential itself is already known for certain viruses. Experimental evidence could be useful to document the absence of recombination in certain viral vectors. Concerning the risks of recombination associated with the administration of several vaccine strains, Mr REYNARD felt that the question was relevant, but that attention should be paid to the degree of detail required in this context, which could quickly be perceived as too onerous without providing any significant benefits to the risk assessment.

Concerning the stability of the GMO, Mr REYNARD indicated that he personally did not see any problem in providing the complete genome sequence of the GMO (most manufacturers already have the sequences), but that it could be difficult to interpret them, mainly because of the intrinsic genetic variability of viral vectors. Mr REYNARD also felt that sequencing for each released batch did not seem appropriate, and would be difficult to implement and analyse. An analysis of stability by sequencing the primary seed batch and the vector after a few passages seemed more appropriate, particularly for medicinal products based on the use of new strains, as the history of use of certain vectors may already be sufficient to consider them stable.

Concerning pharmacovigilance, Mr REYNARD stated that he thought it was appropriate for biomolecular analyses to be recommended in certain cases for medicines containing GMOs.

Lastly, looking ahead, Mr REYNARD indicated that he did not envisage any major changes in the vectors used. On the other hand, new attenuated strains used in live vaccines could emerge and pose a greater risk, in the event of reversion of virulence for example. Gene therapy medicinal products, which are expensive, could also emerge for certain niche markets.

Outside the framework of the interview, Mr REYNARD also indicated that there was an inconsistency between the regulations on GMOs and MOTs (micro-organisms and toxins), leading to certain vectors being considered as MOTs after recombination, regardless of the actual danger associated with them, and called for further discussions on these topics between the institutions concerned to enable the regulations to be changed.

2.5 Hearing with Éric QUÉMÉNEUR (Scientific Director, Transgene) and Julien ROMANETTO (Regulatory Affairs Officer, Transgene)

By way of introduction, Mr QUÉMÉNEUR stated that he was Scientific Director of Transgene, and Mr ROMANETTO that he was in charge of regulatory affairs for Transgene, as well as coordinator of France Biotech's "Advanced Therapy Medicines" working group. Mr

QUÉMÉNEUR also pointed out that Transgene's expertise mainly concerned the development of recombinant viral vectors used in oncology.

Following a reminder of ANSES's missions and the WG's objectives, Mr ROMANETTO indicated the importance of harmonised risk assessment of medicinal products containing GMOs between the different Member States of the European Union, and that a legislative review proposal currently under discussion at European level could lead to all clinical trials being considered by the regulations as cases of deliberate release (in France, clinical trials are currently considered as contained use).

Concerning mitigation mechanisms, Mr QUÉMÉNEUR and Mr ROMANETTO indicated that they were used to providing this information for clinical trial authorisation applications, via existing literature or scientific papers produced by the company, and that the production of specific experimental information seemed justified. Similarly, Mr QUÉMÉNEUR and Mr ROMANETTO indicated that the request for complete sequencing of the genome seemed appropriate in the context of molecular characterisation of the vector. In response to a question from Mr KLONJKOWSKI, Mr QUÉMÉNEUR explained that Transgene assessed the genetic stability of the vector at an early stage in the medicinal product development process, according to a quantitative criterion (90-95% of clones genetically stable after 3 to 5 *in vitro* culture passages), to avoid going ahead with the manufacture of products with poor stability. It should be noted, however, that complete sequencing is not always performed for batch release, but may be used on a case-by-case basis for certain products, both for the molecular characterisation of the product and to verify its purity.

Concerning the assessment of shedding, Mr QUÉMÉNEUR and Mr ROMANETTO indicated that for Transgene, this analysis was generally based on qPCR experiments. Mr QUÉMÉNEUR added that an assessment based on the presence of infectious particles also seemed appropriate, but Mr ROMANETTO pointed out that at European level, there is currently no evidence suggesting that this analysis should be based on the detection of genetic material or infectious particles. Following a statement by Mr KLONJKOWSKI on the advisability of assessing shedding from platform technologies, Mr QUÉMÉNEUR and Mr ROMANETTO commented that they were in favour of the idea of platform technology being taken into account in the pre-clinical and clinical assessment of medicinal products containing GMOs, and hoped that collaborative work could be carried out on the risk of shedding by vector class.

Concerning purification methods and the maximum threshold for plasmid DNA contamination of batches, Mr QUÉMÉNEUR and Mr ROMANETTO stated that the purification process is well documented in the complete authorisation application dossiers, but may not be included in the parts on GMO release due to the section headings. On the other hand, Mr ROMANETTO pointed out that plasmid DNA contamination is not routinely checked when batches are released. Concerning the risks of vertical transmission and their management, Mr ROMANETTO reiterated that this information was indeed included in the complete dossier.

In response to a question from Ms TROADEC on the medium-term outlook for the development of new classes of medicinal products, Mr QUEMÉNEUR indicated that medicinal products obtained by synthetic biology, such as chimeric viruses, could emerge in the medium term.

ANNEX V – REQUEST TO EFSA'S FOCAL POINT NETWORK AND REPLIES FROM MEMBER STATES

ENGAGEMENT AND COOPERATION UNIT

efsa European Food Safety Authority FOCAL POINT

REQUEST FOR EXCHANGE OF INFORMATION

REQUEST DETAILS	
Requesting institution	ANSES
Country	France
Date of request	**09/12/2022**
Title of request	**Environmental risk assessment of medicinal products (human or veterinary) containing genetically modified organisms**
Description of request (including background)	**According to Directive 2001/18/EC of the European Parliament and of the Council on the deliberate release into the environment of genetically modified organisms, EU member states are given the opportunity to communicate comments to the EMA on the environmental risk assessment report provided by companies willing to place medicinal products containing GMOs on the market.** **In this context, the French Agency for Food, Environmental and Occupational Health & Safety is willing to elaborate guidelines to ease the management of these dossiers and complete the available EMA guidelines[1,2,…] with technical requirements.** **We thus would like to know if other EU countries have conducted a similar approach, or refer to guidelines other than the ones provided by the EMA to applicants in order to formulate their comments.** **[1] Guideline on environmental risk assessment for medicinal products consisting of, or containing, genetically modified organisms (EMEA/CHMP/BWP/473191/2006 – Corr)** **[2] Guidance on environmental risk assessment for veterinary medicinal products consisting of or containing genetically modified organisms - European Commission (2017), in *The Rules Governing Medicinal Products in the European Union*, Vol. 6 - Notice to applicants and regulatory guidelines for medicinal products for veterinary use.**
Deadline for submission of replies	**10/02/2023**
Remit(s) of request More than one option can be listed	**Biological hazards (BIOHAZ)** **Genetically Modified Organisms (GMO)** **Other area falling within EFSA's remit: Environmental risk assessment** **Not within EFSA's remit**
Request concern(s)	**Risk assessment** **Risk management**

Countries consulted: Albania, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Iceland, Ireland, Italy, Kosovo, Latvia, Lithuania, Luxembourg, Malta, Montenegro, North Macedonia, Norway, Poland, Portugal, Romania, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, The Netherlands, Turkey, United Kingdom.

Replies received: Austria, Bulgaria, Croatia, Cyprus, Czech Republic, Hungary, Ireland, Italy, Slovak Republic, Spain, The Netherlands.

ANNEX VI – GUIDELINES FOR ASSESSING MEDICINAL PRODUCTS FOR HUMAN USE CONTAINING GENETICALLY MODIFIED REPLICATING VIRAL VECTORS[7]

Technical dossier		**GL-MED-GMO WG's guidelines**	
Sections	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
1.1. Identification of the applicant.	Organisation Name: Address Details: Contact person: Telephone No: Email Address:	No additional recommendation	/
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:	Not applicable in the context of an MA application	/
1.3 Identification of the manufacturer of the clinical vector.	Organisation Name: Manufacturing location:	No additional recommendation	/
2.1 Which virus was used as the parental virus in the construction of the clinical vector?	Scientific name: Strain and isolate: Other names (e.g. commercial name): Biosafety classification*: Parental virus attenuated: Yes // No *Explain if the classification varies between different territories in which the clinical trial will take place.	The parental virus to be considered should correspond to a non-genetically modified initial strain. If the parental virus is genetically modified, the applicant should also describe the corresponding non-genetically modified virus. For France, the classification chosen should correspond to that described in the Order of 16 November 2021 establishing the list of biological pathogens.	

[7] These guidelines are not regulatory in nature, but reflect the requirements or recommendations of ANSES's expert groups as part of their work assessing the environmental risks associated with the release of medicinal products containing GMOs.

Technical dossier		**GL-MED-GMO WG's guidelines**	
Sections	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
2.2. Phenotypic and Genetic Markers.	Briefly describe the most relevant phenotypic and genetic markers of the parental virus, including information on the viral genome size and the packaging limit of the parental virus.	The applicant should provide a precise description of the phenotypic and genetic markers associated with the viral cycle of the parental virus.	The WG believes that knowledge of these characteristics is needed for assessing the capacity for and ease of release of the GMO, particularly in the event of modification of the replication properties of the viruses contained in the medicinal product or co-infection with other viruses.
2.3. What is the host range of the parental virus?	Describe the hosts in which the parental virus naturally occurs, also including hosts that serve as a reservoir. For each possible host, indicate the tissue and cell tropism. If natural hosts of the parental virus include humans, provide available information about the seroprevalence in the EU.	When known, the cell receptor(s) should be specified. Where the parental virus is an attenuated strain, the tropism of the attenuated strain and the wild strain should be specified.	The WG believes that knowledge of these characteristics is needed for assessing the capacity for and ease of release of the GMO, particularly in the event of modification of the replication properties of the viruses contained in the medicinal product or co-infection with other viruses.
2.4. Zoonotic potential of the parental virus.	This Section needs not be filled in case of replication incompetent clinical viral vectors. If humans are not natural hosts of the parental virus, provide information on the zoonotic potential of the parental virus. Describe also the natural geographic distribution of the parental virus and indicate if the parental virus is endemic in the EU.	The risk of transmission from humans to other animals should also be specified (to be discussed depending on the dossier).	/

Technical dossier		**GL-MED-GMO WG's guidelines**	
Sections	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
2.5. Replication properties of the parental virus.	Provide information about the replication of the parental virus. Indicate where replication takes place (cell nucleus, cytoplasma). Is the parental virus capable of establishing latency in the natural host? What are the sequence elements involved in the reactivation process? Provide also any available information on the potential for homologous/non-homologous genomic recombination occurring in nature between viral genomes of the parental virus and related strains or members of the same viral (sub)family.	The applicant should provide a detailed description of the viral cycle of the parental virus, specifying in particular the length of the cycle and giving a sufficient description of any steps in the integration of the virus.	The WG believes that knowledge of these characteristics is needed for assessing the capacity for and ease of release of the GMO, particularly in the event of modification of the replication properties of the viruses contained in the medicinal product or co-infection with other viruses.
2.6. What are the pathogenic properties of the parental virus and what are the available treatment methods?	Describe any pathogenic properties of the parental virus. Where relevant, provide information on pathogenic properties of the parental virus in vulnerable groups such as immunosuppressed individuals, pregnant women and small children. Describe the symptoms caused by the parental virus. Indicate also if therapeutic/prophylactic treatments exist to treat/prevent such an infection.	Clinical signs suggestive of infection by the parental virus should be specified, and distinguished from general clinical signs.	
2.7. Provide relevant data on attenuation and biological restrictions of the parental virus.	If the parental virus is an attenuated/restricted virus, the basis for attenuation/restriction should be described. Describe the conditions (steps) needed for reversion of the attenuation/restriction and the factors that may affect reversion.	The applicant should refer to the existing scientific literature describing the restriction or attenuation mechanism involved, or demonstrate this experimentally.	The WG believes that knowledge of these characteristics is needed for assessing the capacity for and ease of release of the GMO, particularly in the event of modification of the replication properties of the viruses contained in the medicinal product or co-infection with other viruses.

Technical dossier		GL-MED-GMO WG's guidelines	
Sections	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
2.8. What are the transmission routes of the parental virus?	Describe possible transmission routes of the virus. Provide information on viral shedding including asymptomatic shedding of the parental virus. In the case of vector-borne viruses (e.g. arboviruses), indicate the geographic location of the vector.	The applicant should recall any known data on the shedding profile and the infective dose of the parental virus. They should also specify whether the parental virus is capable of crossing the placental or haemato-testicular barriers, and whether cases of vertical transmission are possible.	The WG believes that knowledge of these characteristics is needed for assessing the capacity for and ease of release of the GMO, particularly in the event of modification of the replication properties of the viruses contained in the medicinal product or co-infection with other viruses.
2.9. Can the parental virus survive outside the host?	Describe all survival options and the survival time of the parental virus under optimal environmental conditions, and describe the factors that may be of influence.	The applicant should recall any known data on the stability of the parental virus, and in particular its half-life, as well as any known data on its decontamination.	The WG believes that knowledge of these characteristics is needed for assessing the capacity for and ease of release of the GMO, particularly in the event of modification of the replication properties of the viruses contained in the medicinal product or co-infection with other viruses.
2.10. Provide a brief description of the manufacturing process of the clinical vector.	Answer this question preferably by using a diagram that describes the various production steps. When using plasmids for the manufacturing of the clinical vector, clear maps of the plasmids showing all the constituent parts of the vector should be provided (i.e. in addition to the “transgene plasmid”, all other plasmids such as helper, packaging and pseudotyping plasmids should be described). Explain if there are overlapping sequences in the plasmids.	The applicant should specify the purification method and the maximum plasmid DNA contamination threshold set for batch release.	/

Technical dossier		GL-MED-GMO WG's guidelines	
Sections	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
2.11. Describe the characteristics of the cell lines in which the clinical vector is produced. Also indicate which of the genetic components of the cell could possibly cause complementation or recombination.	The characteristics of all cell lines used and eventual modifications of the cell genome should be explained. Describe the cell types concerned as well as their origin (e.g. human kidney, epithelial cells). The possibility of the genetic material in the cells/cell lines causing a certain interaction with the clinical vector, such as by complementation or recombination should be discussed. Explain if there is a risk of clinical vector modification by trans-complementing sequences. Provide also a description of the identity of these sequences. This can be done on the basis of bioinformatic analysis, such as sequence analysis, alignments or phylogenetic analysis.	No additional recommendation	/
2.12. Contaminating replication-competent virus.	For replication-deficient and conditionally replication-competent clinical vectors, strategies to avoid the generation of replication-competent virus (RCV) should be described. Test methods for detection of replication-competent virus should be described, including information on the specificity and sensitivity thereof. Data from RCV testing at different manufacturing steps should be provided (e.g. virus seed bank, final product). Release criteria with regard to RCV testing should be specified.	This section should be completed for any dossier relating to a genetically modified replicating virus. Data on detection methods and the contamination threshold when batches are released should also be provided.	The WG points out that for this section, applicants often confine themselves to a review of the literature, without any real assessment in the context of the GMO medicinal product. The WG proposes that broader discussions be held with the other French and European bodies responsible for assessing these medicines, in order to define the appropriate tests to be carried out, given the importance of this issue and the growing development of applications involving genetically modified viral vectors.
2.13. Provide a diagram (‘map’) of the clinical vector.	/	No additional recommendation	/

Technical dossier		**GL-MED-GMO WG's guidelines**	
Sections	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
2.14. Molecular characterisation of the clinical vector(s).	Provide the annotated sequence of the complete genome (i.e. indicate the location of the sequences encoding the transgene expression cassette(s) and its regulatory elements). As a minimum, the sequence of the elements that could affect the replication ability, host range, tropism, ability to survive outside the host, route of transmission or pathogenic potential of the clinical vector should be provided. Describe in what way the clinical vector deviates from the parental virus at the level of molecular characterisation. Available data supporting genetic stability of the clinical vector should be provided. Deviations should be discussed, in particular the biological significance thereof.	The applicant should provide a molecular analysis corresponding to the entire genome and its stability (over a number of passages appropriate to the size of the seed batches, and at least equivalent to the maximum number of passages for the master seed), and specifically describe any elements relating to the strain's tropism or virulence.	The WG believes it important to provide a molecular analysis of the entire genome, in order to ensure in particular that modifications have not appeared in the viral genome that could alter its biological properties. Sequencing solely at the genetic engineering site would therefore be considered insufficient.
2.15. Describe the coding genes and the regulatory sequences present in the clinical vector backbone and in the DNA inserted.	A full description must be provided of the inserted or deleted genetic material, also discussing the functions of the sequences, for example: o Expression cassette, including promoter, terminator, and enhancer sequences. o Transgene: e.g. is the expressed product toxic or otherwise harmful to humans (other than the clinical trial subject) or other hosts? Does the transgene provide an advantage for replication/ survival of the clinical vector (vis-à-vis parental virus) or alter the transmission route? o Whether the DNA inserted into the clinical vector contains elements of which the origin or function is unknown. o Whether the clinical vector contains elements that are not specifically intended for the therapeutic functions.	No additional recommendation	/

Technical dossier		GL-MED-GMO WG's guidelines	
Sections	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
2.16. Differences between the biological profile of the clinical vector and the parental virus.	Indicate whether the clinical vector particles are pseudotyped and whether the envelope is provided in trans. Explain differences that exist between the clinical vector and the parental virus regarding: o Host range, including host specificity and the tissue and cell tropism. o Transmission route. o Pathogenic properties. Where relevant, consider potential effects in common population and in vulnerable groups such as immunosuppressed individuals, pregnant women, small children, or any other group with a higher risk. o Ability to survive outside the host. If available, provide data on the loss of infectivity of the clinical vector on different materials or in liquids (e.g. waste water).	The applicant should provide a detailed description of any change in the strain's tropism or virulence.	The WG believes that knowledge of these characteristics is needed for assessing the capacity for and ease of release of the GMO, particularly in the event of modification of the replication properties of the viruses contained in the medicinal product or co-infection with other viruses.
2.17. Potential for recombination with the parental virus in vivo and description of potential recombinants.	Discuss the potential for homologous recombination in vivo and describe all recombinants that might be generated by homologous recombination with e.g. the parental virus. Discuss the potential biological (including pathogenic) effects of any possible recombination for the population (including for vulnerable groups). Indicate whether the recombinants described have been monitored and detected in previous experiments or after administration to humans.	No additional recommendation	/

Technical dossier		**GL-MED-GMO WG's guidelines**	
Sections	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
2.18. Biodistribution and shedding.	Detailed data on vector shedding (including information on the administered dose, the route of administration, and – where available – immune status of the treated subjects) from previous clinical trials with the clinical vector should be provided. Where available and if relevant for the environmental risk assessment, biodistribution data should be provided. If there is no prior clinical experience with the same clinical vector, the potential for shedding should be discussed based on non-clinical data and/or clinical experience from related clinical vectors. If the applicant relies on data from related clinical vectors, the relevance of the data to the product that is the object of this application should be explained considering, in particular, the dose and route of administration. When shedding occurs, the estimated duration should be specified. The methods used for detection of viral shedding including information on the specificity (including ability to detect revertants) and sensitivity thereof should be provided.	In particular, the applicant should mention any known data on the detection of infectious particles and any clinical data previously obtained, and specify in each case the sensitivity and specificity of the tests used. The applicant should also specify the risk of vertical transmission of infectious particles. Lastly, the applicant should link the observations made (in particular where the particles circulate and the shedding duration) to the measures taken to prevent release in the environment (Section 3.6).	The WG considers that data enabling the detection of infectious particles and the presentation of clinical data are the most informative for assessing the risk of shedding.

Technical dossier		**GL-MED-GMO WG's guidelines**	
Sections	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
3.1. General information about the clinical trial.	EudraCT-number (where available): Deliberate release reference number (where available and applicable): Title of the clinical trial: Name of principal investigator: This information may be provided in the annex with confidential information. 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, identify the countries concerned:	The applicant should mention all the clinical studies carried out on the medicinal product concerned by the MA application, as well as any prior authorisation for use. The applicant may also indicate the identity of the sponsor and the investigation sites for each clinical study.	
3.2. Intended location(s) of the study.	The applicant should provide information about the clinical sites located in the country of submission of the application. The following additional information should be provided: § the location(s) of laboratories (in the country of submission) in which activities with the GMO are carried out under the framework of the clinical trial application should be stated. § information about the location where the investigational medicinal product is stored (to the extent that the location is in the country of submission but outside the clinical site). § information about the location where patient's samples that contain GMO's are stored (to the extent that the location is in the country of submission but outside the clinical site).	Not applicable in the context of an MA application	/

Technical dossier		**GL-MED-GMO WG's guidelines**	
Sections	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
3.3. Storage of the clinical vector at the clinical site.	The applicant should provide information about the storage location, conditions of storage (including restrictions of access), and the maximal storage duration. The applicant should specify if the dose is being prepared in the hospital pharmacy. If the clinical dose is prepared at a location other than the hospital pharmacy, this should be explained.	Not applicable in the context of an MA application	/
3.4. Logistics for on-site transportation of the clinical vector.	The applicant should provide information about the logistics for in-house transportation (i.e. transfer of the clinical vector from storage to the administration site and –where applicable- site where dose is prepared). The applicant should provide information about the characteristics of the containers used addressing also disinfection procedures applied and labelling of the containers.	Not applicable in the context of an MA application	/
3.5. Information about reconstitution, finished medicinal product and administration to patients.	Reconstitution (where applicable, summarise reconstitution steps): Pharmaceutical form and strength: Mode of administration: Information on dosing and administration schedule (in case of repeated dosing): Information on concomitant medication that may affect the shedding of the clinical vector/ environmental risks (e.g. administration of laxatives, administration of a medicinal product that could enhance the replication activity of the clinical vector, administration of a plasmid-based medicinal product):	No additional recommendation	

Technical dossier		**GL-MED-GMO WG's guidelines**	
Sections	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
3.6 Measures to prevent dissemination into the environment.	a) Control measures during reconstitution (if applicable), handling and administration. b) Personal protective equipment. c) Decontamination/cleaning measures after administration or in the case of accidental spilling (i.e. decontamination /cleaning measures of potentially contaminated materials, surfaces and areas). In addition, the disinfection procedures applied should be justified by providing evidence that the chosen method is sufficiently active against the clinical vector. d) Elimination or inactivation of left-overs of the finished product at the end of the clinical trial. e) Waste treatment (including also –where applicable- decontamination and disposal of potentially contaminated waste that accumulates outside the clinical trial site). Where applicable, identify also the company responsible for waste management. f) Are there exclusion criteria applied to the enrolment of patients in the clinical trial to address environmental risks? Are the treated patients subject to restrictions after administration of the product? g) Recommendations given to clinical trial subjects to prevent dissemination. h) Recommendations on donation of blood/cells/tissues/organs by the clinical trial subject. i) Other measures.	The applicant should endeavour to link the proposed management measures to the observed biodistribution and shedding data (Section 2.18), particularly in terms of the duration of applicability of these measures. Where appropriate, the applicant should propose specific contraception measures. Lastly, the applicant should also aim to take account of specific populations (the immuno-compromised or those suffering from the same disease as the patient, for example) and the patient's immediate environment. In addition, it should be remembered that in the context of an MA, patients should be indefinitely excluded from donating blood, plasma, cells, tissues or organs.	

Technical dossier		GL-MED-GMO WG's guidelines	
Sections	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
3.7. Sampling and further analyses of samples from study subjects.	This Section should be filled in where samples that may contain GMOs are being taken from patients in the context of the clinical trial. a) Describe how samples will be handled/stored/transported. To the extent that handling/ storage and transport of samples are treated under same procedures as the clinical vector, cross-reference can be made as appropriate. b) Indicate whether and at which time points samples that may contain the administered clinical vector are taken from study subjects. c) If samples are stored at the clinical site, describe storage location and storage conditions. d) Explain if there is any non-routine* testing of the samples and indicate whether the clinical vector is generated de novo during the testing. *Standard clinical care tests as well as tests required to fulfil long-term follow-up of clinical trial subjects need not be mentioned.	Not applicable in the context of an MA application	/
3.8 Emergency response plans.	Emergency response plans for accidental self-administration during handling or administering the clinical vector: Emergency response plans for accidental release into the environment of the clinical vector:	No additional recommendation	/
4.1. Plan of the site(s) concerned.	Applicants should provide a copy of the plan of the site where the clinical trial takes place.	Not applicable in the context of an MA application	/
4.2 Other information.	/	Not applicable in the context of an MA application	/

ERA		GL-MED-GMO WG's guidelines	
Subsection	***Explanation available in the "common application form"***	***Recommendation of the GL-MED-GMO WG***	***Justification***
5.1. Risks to healthcare professionals and/or close contacts of the clinical trial subject - Hazard identification	Provide a list of the potential adverse effects (e.g. immune reaction, integration in the genome of the exposed cells, adverse effects linked to the expression of the therapeutic gene, etc.) if transmission of the clinical vector or potential revertants to thirds -including vulnerable groups- occurs through shedding (as described in Section 2.18).	No additional recommendation; the applicant may refer to the documents *Guideline on environmental risk assessments for medicinal products consisting of, or containing, genetically modified organisms* (EMEA/CHMP/BWP/473191/2006 – Corr) and *Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products* (EMEA/CHMP/GTWP/125491/2006).	/
5.2. Risks to healthcare professionals and/or close contacts of the clinical trial subject - Hazard characterisation	Provide an estimate of the magnitude of each of the identified potential adverse effects (it should be assumed that each of the hazards will occur). Where a quantitative estimation is not possible, a category (“high”, “moderate”, “low” or “negligible”) should be assigned.	No additional recommendation; the applicant may refer to the documents *Guideline on environmental risk assessments for medicinal products consisting of, or containing, genetically modified organisms* (EMEA/CHMP/BWP/473191/2006 – Corr) and *Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products* (EMEA/CHMP/GTWP/125491/2006).	/
5.3. Risks to healthcare professionals and/or close contacts of the clinical trial subject - Exposure characterisation	Provide an estimate of the likelihood (probability) that each of the identified hazards will occur. Where a quantitative estimation is not possible, a category (“high”, “moderate”, “low” or “negligible”) should be assigned.	No additional recommendation; the applicant may refer to the documents *Guideline on environmental risk assessments for medicinal products consisting of, or containing, genetically modified organisms* (EMEA/CHMP/BWP/473191/2006 – Corr) and *Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products* (EMEA/CHMP/GTWP/125491/2006).	/

ERA		GL-MED-GMO WG's guidelines	
Subsection	***Explanation available in the "common application form"***	***Recommendation of the GL-MED-GMO WG***	***Justification***
5.4. Risks to healthcare professionals and/or close contacts of the clinical trial subject - Risk characterisation	Considering the magnitude of each of the effects identified and the likelihood of their occurrence, characterise the risk. Where a quantitative estimation is not possible, a category ("high", "moderate", "low" or "negligible") should be assigned.	No additional recommendation; the applicant may refer to the documents *Guideline on environmental risk assessments for medicinal products consisting of, or containing, genetically modified organisms* (EMEA/CHMP/BWP/473191/2006 – Corr) and *Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products* (EMEA/CHMP/GTWP/125491/2006).	/
5.5. Risks to healthcare professionals and/or close contacts of the clinical trial subject - Risk management strategies	The applicant should explain measures implemented to reduce the potential risks to thirds and/or the environment associated with the clinical use of the clinical vector. This includes -but is not limited to- the measures implemented to prevent the risks of accidental transfer during reconstitution, handling, administration of the product, or during manipulation of patient's samples (after administration of the clinical vector). The applicant should also explain the recommendations that will be provided to the clinical trial subject and/or close contacts to prevent dissemination/accidental contamination. Finally, the applicant should consider if clinical trial subjects should be prevented from donating blood/cells/ tissues/ organs after being administered the clinical vector. This information should be listed in Section 3.6.	No additional recommendation; the applicant may refer to the documents *Guideline on environmental risk assessments for medicinal products consisting of, or containing, genetically modified organisms* (EMEA/CHMP/BWP/473191/2006 – Corr) and *Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products* (EMEA/CHMP/GTWP/125491/2006).	/
5.6. Risks to the environment - Hazard identification	Provide a list of the potential adverse effects. As appropriate, consider specific environmental conditions that may affect the survival, replication or ability to colonise (wind, water, soil, temperatures, pH, etc.).	At the very least, the applicant should indicate that there are no environmental risks and justify this or, where appropriate, specify them.	The WG believes that the absence of risk to the environment is not evident for medicinal products containing genetically modified viral vectors (other than AAV), given the variety of possible parental viruses.

ERA		GL-MED-GMO WG's guidelines	
Subsection	***Explanation available in the "common application form"***	***Recommendation of the GL-MED-GMO WG***	***Justification***
5.7. Risks to the environment - Hazard characterisation	Provide an estimate of the magnitude of each of the identified potential adverse effects (it should be assumed that each of the hazards will occur). Where a quantitative estimation is not possible, a category (“high”, “moderate”, “low” or “negligible”) should be assigned.	No additional recommendation; the applicant may refer to the documents *Guideline on environmental risk assessments for medicinal products consisting of, or containing, genetically modified organisms* (EMEA/CHMP/BWP/473191/2006 – Corr) and *Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products* (EMEA/CHMP/GTWP/125491/2006). If there are no identified risks to the environment, this section does not need to be completed.	/
5.8. Risks to the environment - Exposure characterisation	Provide an estimate of the likelihood (probability) that each of the identified hazards will occur. Where a quantitative estimation is not possible, a category (“high”, “moderate”, “low” or “negligible”) should be assigned.	No additional recommendation; the applicant may refer to the documents *Guideline on environmental risk assessments for medicinal products consisting of, or containing, genetically modified organisms* (EMEA/CHMP/BWP/473191/2006 – Corr) and *Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products* (EMEA/CHMP/GTWP/125491/2006). If there are no identified risks to the environment, this section does not need to be completed.	/

ERA		GL-MED-GMO WG's guidelines	
Subsection	***Explanation available in the "common application form"***	***Recommendation of the GL-MED-GMO WG***	***Justification***
5.9. Risks to the environment - Risk characterisation	Considering the magnitude of each of the effects identified and the likelihood of their occurrence, characterise the risk. Where a quantitative estimation is not possible, a category (“high”, “moderate”, “low” or “negligible”) should be assigned.	No additional recommendation; the applicant may refer to the documents *Guideline on environmental risk assessments for medicinal products consisting of, or containing, genetically modified organisms* (EMEA/CHMP/BWP/473191/2006 – Corr) and *Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products* (EMEA/CHMP/GTWP/125491/2006). If there are no identified risks to the environment, this section does not need to be completed.	/
5.10. Risks to the environment - Risk management strategies	The applicant should implement adequate measures to prevent dissemination into the environment. These should be listed in Section 3.6.	No additional recommendation; the applicant may refer to the documents *Guideline on environmental risk assessments for medicinal products consisting of, or containing, genetically modified organisms* (EMEA/CHMP/BWP/473191/2006 – Corr) and *Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products* (EMEA/CHMP/GTWP/125491/2006). If there are no identified risks to the environment, this section does not need to be completed.	/
5.11. Overall risk evaluation and conclusions	Evaluate the overall risk of the clinical vector for humans (healthcare professionals and close contacts of the patient) and the environment considering, as applicable, the risk management strategies described in Section 3.6.	No additional recommendation; the applicant may refer to the documents *Guideline on environmental risk assessments for medicinal products consisting of, or containing, genetically modified organisms* (EMEA/CHMP/BWP/473191/2006 – Corr) and *Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products* (EMEA/CHMP/GTWP/125491/2006). If there are no identified risks to the environment, this section does not need to be completed.	/

ANNEX VII – GUIDELINES FOR ASSESSING MEDICINAL PRODUCTS FOR HUMAN USE CONTAINING GENETICALLY MODIFIED ADENO-ASSOCIATED VIRAL VECTORS[8]

Technical dossier		GL-MED-GMO WG's guidelines	
Sections	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
1.1. Identification of the applicant.	Organisation Name: Address Details: Contact person: Telephone No: Email Address:	No additional recommendation	/
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:	Not applicable in the context of an MA application	/
1.3 Identification of the manufacturer of the clinical vector.	Organisation Name: Manufacturing location:	No additional recommendation	/

[8] These guidelines are not regulatory in nature, but reflect the requirements or recommendations of ANSES's expert groups as part of their work assessing the environmental risks associated with the release of medicinal products containing GMOs.

Technical dossier		GL-MED-GMO WG's guidelines	
Sections	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
2.1 Description of the production system.	Clear maps of the vectors used for recAAV production (e.g. plasmids, baculoviruses) showing all the constituent parts of the AAV clinical vector should be provided (i.e. in addition to the “transgene vector”, all other vectors such as helper, packaging and pseudotyping vectors should be described). The characteristics of all cell lines used and eventual modifications of the cell genome should be explained. Describe the cell type(s) concerned as well as their origin (e.g. human kidney, epithelial cells, insect cells). The possibility of the genetic material in the cells/cell lines causing a certain interaction with the clinical vector, such as by complementation or recombination should be discussed. In particular, the tests applied to identify possible contamination of the cell line by wild-type AAV viruses and/or any virus identified as helper virus for AAV should be explained.	The applicant should specify the purification method and the maximum plasmid DNA contamination threshold set for batch release.	The WG believes this information to be important, as the presence of rep and cap contaminants can encourage the formation of replication-competent viruses.
2.2. Demonstration of absence of formation of replication-competent virus.	The risk of generation of a replication competent AAV through recombination of the constituent parts of the viral vector system should be minimised. Test methods for detection of replication-competent virus should be described including information on the specificity and sensitivity thereof. Data from RCV testing at different manufacturing steps should be provided (e.g. virus seed bank, final product). Release criteria with regard to RCV testing should be specified.	This section should be completed for any dossier relating to a genetically modified AAV vector. Data on detection methods and the contamination threshold when batches are released should also be provided.	The WG points out that for this section, applicants often confine themselves to a review of the literature, without any real assessment in the context of the GMO medicinal product. The WG proposes that broader discussions be held with the other French and European bodies responsible for assessing these medicines, in order to define the appropriate tests to be carried out, given the importance of this issue and the growing development of applications involving genetically modified viral vectors.

Technical dossier		**GL-MED-GMO WG's guidelines**	
Sections	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
2.3. Provide a diagram (‘map’) of the clinical vector.	/	No additional recommendation	/
2.4. Molecular characterisation of the clinical vector	Provide the annotated sequence of the genome (i.e. indicate the location of the sequences encoding the transgene expression cassette(s) and its regulatory elements). Describe in what way the clinical vector deviates from the parental virus at the level of molecular characterisation. Available data supporting genetic stability of the clinical vector should be provided. Deviations should be discussed, in particular the biological significance thereof.	The applicant should provide a molecular analysis corresponding to the entire genome and its stability (over a number of passages appropriate to the size of the seed batches, and at least equivalent to the maximum number of passages for the master seed).	The WG believes that knowledge of these characteristics is needed for assessing the capacity for and ease of release of the GMO.
2.5. Description of the insert	The expression cassette e.g. transgene, including regulatory and coding sequences, should be described. In particular, it should be explained if the expressed product is toxic or otherwise harmful to humans (other than the clinical trial subject) or other hosts. Additionally, if the applicant considers that the transgene could confer any advantage for replication/survival of the clinical vector (vis-à-vis the parental virus), this should be explained.	No additional recommendation	/

Technical dossier		GL-MED-GMO WG's guidelines	
Sections	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
2.6. Biodistribution and shedding	Detailed data on clinical vector shedding (including information on the administered dose, the route of administration, and –where available- immune status of the treated subjects) from previous clinical trials with the clinical vector should be provided. Where available and if relevant for the environmental risk assessment, biodistribution data should be provided. If there is no prior clinical experience with the same clinical vector, the potential for shedding should be discussed based on non-clinical data and/or clinical experience from related clinical vectors. If the applicant relies on data from related clinical vectors, the relevance of the data to the product that is the object of this application should be explained considering, in particular, the dose and route of administration. When shedding occurs, the estimated duration should be specified. The methods used for detection of viral shedding, including information on the specificity and sensitivity thereof, should be provided.	In particular, the applicant should mention any known data on the detection of infectious particles and any clinical data previously obtained, and specify in each case the sensitivity and specificity of the tests used. The applicant should also specify the risk of vertical transmission of infectious particles. Lastly, the applicant should link the observations made (in particular where the particles circulate and the shedding duration) to the measures taken to prevent release in the environment (Section 3.6).	The WG considers that data enabling the detection of infectious particles and the presentation of clinical data are the most informative for assessing the risk of shedding. The WG also believes that a section on the risk of AAV integration into the genome should be added to the form, particularly in view of the risk of reactivation in the event of subsequent infection by a helper virus.
3.1. General information about the clinical trial.	EudraCT-number (where available): Deliberate release reference number (where available and applicable): Title of the clinical trial: Name of principal investigator: This information may be provided in the annex with confidential information. 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, identify the countries concerned:	The applicant should mention all the clinical studies carried out on the medicinal product concerned by the MA application, as well as any prior authorisation for use. The applicant may also indicate the identity of the sponsor and the investigation sites for each clinical study.	

Technical dossier		**GL-MED-GMO WG's guidelines**	
Sections	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
3.2. Intended location(s) of the study.	The applicant should provide information about the clinical sites located in the country of submission of the application. The following additional information should be provided: § the location(s) of laboratories (in the country of submission) in which activities with the GMO are carried out under the framework of the clinical trial application should be stated. § information about the location where the investigational medicinal product is stored (to the extent that the location is in the country of submission but outside the clinical site). § information about the location where patient's samples that contain GMO's are stored (to the extent that the location is in the country of submission but outside the clinical site).	Not applicable in the context of an MA application	/
3.3. Storage of the clinical vector at the clinical site.	The applicant should provide information about the storage location, conditions of storage (including restrictions of access), and the maximal storage duration. The applicant should specify if the dose is being prepared in the hospital pharmacy. If the clinical dose is prepared at a location other than the hospital pharmacy, this should be explained.	Not applicable in the context of an MA application	/
3.4. Logistics for on-site transportation of the clinical vector.	The applicant should provide information about the logistics for in-house transportation (i.e. transfer of the clinical vector from storage to the administration site and –where applicable- site where dose is prepared). The applicant should provide information about the characteristics of the containers used addressing also disinfection procedures applied and labelling of the containers.	Not applicable in the context of an MA application	/

Technical dossier		GL-MED-GMO WG's guidelines	
Sections	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
3.5. Information about reconstitution, finished medicinal product and administration to patients.	Reconstitution (where applicable, summarise reconstitution steps): Pharmaceutical form and strength: Mode of administration: Information on dosing and administration schedule (in case of repeated dosing): Information on concomitant medication that may affect the shedding of the clinical vector/ environmental risks (e.g. administration of laxatives, administration of a medicinal product that could enhance the replication activity of the clinical vector, administration of a plasmid-based medicinal product):	No additional recommendation	/
3.6 Measures to prevent dissemination into the environment.	a) Control measures during reconstitution (if applicable), handling and administration. b) Personal protective equipment. c) Decontamination/cleaning measures after administration or in the case of accidental spilling (i.e. decontamination /cleaning measures of potentially contaminated materials, surfaces and areas). In addition, the disinfection procedures applied should be justified by providing evidence that the chosen method is sufficiently active against the clinical vector. d) Elimination or inactivation of left-overs of the finished product at the end of the clinical trial. e) Waste treatment (including also –where applicable- decontamination and disposal of potentially contaminated waste that accumulates outside the clinical trial site). Where applicable, identify also the company responsible for waste management. f) Are there exclusion criteria applied to the enrolment of patients in the clinical trial to address environmental risks? Are the treated patients subject to restrictions after administration of the product? g) Recommendations given to clinical trial subjects to prevent dissemination. h) Recommendations on donation of blood/cells/tissues/organs by the clinical trial subject. i) Other measures.	The applicant should endeavour to link the proposed management measures to the observed biodistribution and shedding data (Section 2.6), particularly in terms of the duration of applicability of these measures. Where appropriate, the applicant should propose specific contraception measures. Lastly, the applicant should also aim to take account of specific populations (the immuno-compromised or those suffering from the same disease as the patient, for example) and the patient's immediate environment. In addition, it should be remembered that in the context of an MA, patients should be indefinitely excluded from donating blood, cells, tissues or organs.	

Technical dossier		**GL-MED-GMO WG's guidelines**	
Sections	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
3.7. Sampling and further analyses of samples from study subjects	This Section should be filled in where samples that may contain GMOs are being taken from patients in the context of the clinical trial. a) Describe how samples will be handled/stored/transported. To the extent that handling/ storage and transport of samples are treated under same procedures as the clinical vector, cross-reference can be made as appropriate. b) Indicate whether and at which time points samples that may contain the administered clinical vector are taken from study subjects. c) If samples are stored at the clinical site, describe storage location and storage conditions. d) Explain if there is any non-routine* testing of the samples and indicate whether the clinical vector is generated de novo during the testing. *Standard clinical care tests as well as tests required to fulfil long-term follow-up of clinical trial subjects need not be mentioned.	Not applicable in the context of an MA application	/
4.1. Plan of the site(s) concerned	Applicants should provide a copy of the plan of the site where the clinical trial takes place.	Not applicable in the context of an MA application	/
4.2 Other information	/	Not applicable in the context of an MA application	/

ERA		**GL-MED-GMO WG's guidelines**	
Section	***Explanation available in the "common application form"***	***Recommendation of the GL-MED-GMO WG***	***Justification***
5. Specific environmental risk assessment	Considering the specific characteristics of the investigational medicinal product (as described in Section 2 of the application form), the applicant considers that the specific environmental risk assessment provided for in Section 2 of the Good Practice on the assessment of GMO related aspects in the context of clinical trials with AAV clinical vectors is applicable: Yes □ No □	No additional recommendation; the applicant may refer to the document *Good Practice on the assessment of GMO related aspects in the context of clinical trials with AAV clinical vectors*.	/

ANNEX VIII – GUIDELINES FOR ASSESSING MEDICINAL PRODUCTS FOR HUMAN USE CONTAINING GENETICALLY MODIFIED CELLS[9]

Technical dossier		**GL-MED-GMO WG's guidelines**	
Section	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
1.1. Identification of the applicant.	Organisation Name: Address Details: Contact person: Telephone No: Email Address:	No additional recommendation	/
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:	Not applicable in the context of an MA application	/
1.3. Information about the clinical trial			

[9] These guidelines are not regulatory in nature, but reflect the requirements or recommendations of ANSES's expert groups as part of their work assessing the environmental risks associated with the release of medicinal products containing GMOs.

Technical dossier		**GL-MED-GMO WG's guidelines**	
Section	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
1.3.a. General information about the clinical trial.	EudraCT-number (where available): Deliberate release reference number (where available and applicable): Title of the clinical trial: Name of principal investigator: 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, identify the countries concerned:	The applicant should mention all the clinical studies carried out on the medicinal product concerned by the MA application, as well as any prior authorisation for use. The applicant may also indicate the identity of the sponsor and the investigation sites for each clinical study.	
1.3.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, the location(s) of laboratories7 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).	Not applicable in the context of an MA application	/
1.3.c. Logistics for on-site transportation of the clinical vector	The applicant should provide information about the logistics for in-house transportation.	Not applicable in the context of an MA application	/
2.1 Characterisation of the finished investigational medicinal product.			

Technical dossier		**GL-MED-GMO WG's guidelines**	
Section	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
2.1.a. General information	Description of the finished medicinal product Autologous □ Allogeneic □ Specify type of cells (e.g. hematopoietic stem cells…): Viral vector used: Retrovirus □ Lentivirus □ Adeno-associated virus (“AAV”) □ If viral vector used is AAV, does the production system of the AAV contain a replication-competent helper virus? Yes □ No □ Human cells genetically modified without the use of a viral vector: Specify transfer system used: Short description of the modifications made to the cells: Pharmaceutical form: Mode of administration:	No additional recommendation	/
2.1.b. Absence of replication competent virus particles in the finished product	The applicant should demonstrate absence of formation of replication competent virus at the level of the viral production system or, alternatively, demonstrate absence of replication competent virus in the finished product in accordance with the Good Practice on the assessment of GMO-related aspects in the context of clinical trials with human cells genetically modified. When a helper virus is used in the production system, the applicant should demonstrate that the finished product does not contain residual helper virus. This may be demonstrated at the level of the viral vector. This section should not be filled in case of human cells genetically modified without the use of a viral vector.	This section should be completed for any dossier relating to a cell modified using a viral vector. Data on detection methods and the contamination threshold when batches are released should also be provided.	The WG points out that for this section, applicants often confine themselves to a review of the literature, without any real assessment in the context of the GMO medicinal product. The WG proposes that broader discussions be held with the other French and European bodies responsible for assessing these medicines, in order to define the appropriate tests to be carried out, given the importance of this issue and the growing development of applications involving genetically modified viral vectors.

2.1.c. Presence of residual infectious viral vector particles in the finished product	The applicant should submit information in accordance with subsection (i) or (ii) as appropriate. This section needs not be filled-in for human cells genetically modified by means of AAVs or in case of human cells genetically modified without a viral vector. (i) Negligible amounts of residual infectious viral vector particles in the finished product: The applicant should demonstrate that residual infectious retro/lentiviral vector particles have been reduced to negligible concentrations in accordance with the Good Practice on the assessment of GMO-related aspects in the context of clinical trials with human cells genetically modified. (ii) Presence of residual infectious viral vector particles in the finished product: If residual infectious retro/lentiviral vector particles have not been reduced to negligible concentrations, the applicant should provide an estimation of the number of residual infectious retro/lentiviral vector particles present in the finished product in accordance with the Good Practice on the assessment of GMO-related aspects in the context of clinical trials with human cells genetically modified. The applicant should also provide evidence (i.e. data -including literature data- and/or sound scientific arguments) to justify that the residual vector particles present in the finished product do not pose more than a negligible risk to the environment. Such evidence may be based on the expected inactivation/clearance of the residual infectious vector particles after administration of the finished product and/or the specific characteristics of the vector used for transduction, including the characteristics of the insert. If environmental risks cannot be excluded, additional risk measures should be put in place and described in Section 3 in order to reduce the environmental risk to a negligible level.	In case (ii), the applicant should specify whether the virus used is capable of crossing the placental or haemato-testicular barriers, and whether cases of vertical transmission are possible.	The WG believes that the residual presence of any transformation tool (RNP or RNA for example), and not just viral particles, should be stated by the applicant.

Technical dossier		GL-MED-GMO WG's guidelines	
Section	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
2.2. Molecular characterisation of the applied vectors			
2.2.a. Map of the construct	/	No additional recommendation	/
2.2.b. Description of each of the components of the vector	Provide information about the replication of the parental virus. Indicate where replication takes place (cell nucleus, cytoplasma). Is the parental virus capable of establishing latency in the natural host? What are the sequence elements involved in the reactivation process? Provide also any available information on the potential for homologous/non-homologous genomic recombination occurring in nature between viral genomes of the parental virus and related strains or members of the same viral (sub)family.	No additional recommendation	/
3.1. Measures to prevent risks of accidental transfer during administration to health care professionals and other staff involved in the transport/handling/administration of the product	The applicant should provide an overview of relevant (hospital hygiene) measures that will be taken, including personal protective equipment and a description of measures to take in case of accidental self-administration of the investigational medicinal product (e.g. needle stick).	The applicant should aim to take account of specific populations (the immuno-compromised or those suffering from the same disease as the patient, for example).	
3.2. Risk minimisation strategies regarding patients	The applicant should explain if it is considered that patients should be prevented from donating blood/cells/tissues/organs after being administered the human cells genetically modified.	Not applicable in the context of an MA application	/

Technical dossier		GL-MED-GMO WG's guidelines	
Section	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
3.3. Measures to prevent dissemination into the environment	Decontamination/cleaning measures after administration: Elimination or inactivation of left-overs of the finished product at the end of the clinical trial: Waste treatment:	No additional recommendation	/
3.4. Other risk minimisation measures	This section should only be completed if the applicant considers that there are additional risk minimisation measures that should be implemented.	If residual infectious particles are still in the cells (Section 2.1.c), the applicant should endeavour to propose appropriate management measures for the patient's immediate environment. Where appropriate, the applicant should propose specific contraception measures. Lastly, the applicant should aim to take account of specific populations (the immuno-compromised or those suffering from the same disease as the patient, for example).	
5.1. Manufacturing site	Organisation Name: Address Details: Contact person: Telephone No: Email Address: License number (if the site is not in the country of application, please indicate the country where the manufacturing takes place): Containment level:	No additional recommendation	

Technical dossier		GL-MED-GMO WG's guidelines	
Section	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
5.2. Application for manufacturing license	This Section should only be completed if the applicant is also responsible for the manufacturing of the investigational medicinal product and seeks authorisation of the manufacturing site responsible for the transduction of the cells or other downstream manufacturing activities.		
5.2.a. Administrative information about the site	Organisation name: Address details: Contact person: Telephone No: Email Address:	Not applicable in the context of an MA application	/
5.2.b. Description of manufacturing operations and risk minimisation measures	Information about the vector production system: The production cell line contains HIV 1 or 2, HTLV 1 or 2, SIV or other relevant retro-lentivirus that could lead to complementation/recombination of the retro/lentiviral vector (relevant for human cells genetically modified by means of retro/lentiviral vectors): Yes □ No □ Cells from HIV/HTLV positive donors are excluded (relevant for human cells genetically modified by means of retro/lentiviral vectors): Yes □ No □ Please provide a detailed description of the each of the components of the vector and characterisation of the critical elements of the helper/packaging vectors. Deviations from the predicted sequences have been identified at the level of molecular characterisation of the applied vectors. In the affirmative, please provide details. Yes □ No □ Description of manufacturing operations Risk minimisation measures	Not applicable in the context of an MA application	/

Technical dossier		**GL-MED-GMO WG's guidelines**	
Section	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
5.2.c. Level of containment	/	Not applicable in the context of an MA application	/
6.1. Plan of the site(s) concerned	/	Not applicable in the context of an MA application	/
6.2. Other information	/	Not applicable in the context of an MA application	/

ERA		GL-MED-GMO WG's guidelines	
Section	***Explanation available in the "common application form"***	***Recommendations of the GL-MED-GMO WG***	***Justifications***
4. Specific environmental risk assessment	Having regard to the specific characteristics of the investigational medicinal product (as described in Section 2) and, where appropriate, the implemented control measures (as described in Section 3) the applicant considers that the specific environmental risk assessment provided for in the Good Practice on the assessment of GMO-related aspects in the context of clinical trials with human cells genetically modified is applicable: Yes □ No □ If the investigational medicinal product consists of human cells genetically modified by means of retro/lentiviral vectors and residual infectious retro/lentiviral vector particles have not been reduced to negligible concentrations in the finished product, the applicant considers, on the basis of the information provided in Section 2.1 (c)(ii) and –where appropriate- any specific risk minimisation measures provided for in Section 3, that the presence of residual viral vector particles in the finished product does not pose more than negligible risks to the environment: Yes □ No □	The applicant should demonstrate that the persistence of the genetically modified cells is not altered by the modification, in particular due to potential off-target effects where applicable. The applicant may also refer to the document *Good Practice on the assessment of GMO-related aspects in the context of clinical trials with human cells genetically modified*.	/

ANNEX IX – GUIDELINES FOR ASSESSING VETERINARY MEDICINAL PRODUCTS CONTAINING GENETICALLY MODIFIED ORGANISMS[10]

Technical dossier	**GL-MED-GMO WG's guidelines**	
Sections	***Recommendations of the GL-MED-GMO WG***	***Justifications***
I – GENERAL INFORMATION		
A. Name and address of the notifier (company or institute).	No specific recommendation	/
B. Names, qualifications and experience of the responsible scientists.	No specific recommendation	/
C. Title of the project.	No specific recommendation	/
II. INFORMATION RELATING TO THE GMO(s)		
A. Characteristics of the a) donor b) recipient or c) (where appropriate) parental organism(s)		
A.1. Scientific name.	No specific recommendation	/
A.2. Taxonomy.	No specific recommendation	/
A.3. Other names (usual name, strain name, etc.).	No specific recommendation	/
A.4. Phenotypic and genetic markers.	The applicant should provide a precise description of the phenotypic and genetic markers associated with the viral cycle of the parental virus.	The WG believes that knowledge of these characteristics is needed for assessing the capacity for and ease of release of the GMO, particularly in the event of modification of the replication properties of the viruses contained in the medicinal product or co-infection with other viruses.
A.5. Degree of relatedness between donor and recipient or between parental organisms.	No specific recommendation	/
A.6. Description of identification and detection techniques.	The technique described should concern an unmodified region in the GMO contained in the medicinal product.	The WG considers that the reliability of the technique should not be diminished by the genetic modification.
A.7. Sensitivity, reliability (in quantitative terms) and specificity of detection and identification techniques.	No specific recommendation	/

[10] These guidelines are not regulatory in nature, but reflect the requirements or recommendations of ANSES's expert groups as part of their work assessing the environmental risks associated with the release of medicinal products containing GMOs.

Technical dossier	**GL-MED-GMO WG's guidelines**	
Sections	***Recommendations of the GL-MED-GMO WG***	***Justifications***
A.8. Description of the geographical distribution and of the natural habitat of the organism, including information on natural predators, preys, parasites, competitors, symbionts and hosts.	Parallels should be drawn between the breeding or habitat areas of the medicinal product's target and non-target species and the geographical distribution of the parental organism.	
A.9. Organisms with which transfer of genetic material is known to occur under natural conditions.	No specific recommendation	/
A.10. Verification of the genetic stability of the organisms and factors affecting it.	No specific recommendation	/
A.11. Pathological, ecological and physiological traits of organisms: a) classification of hazard according to existing Community rules concerning the protection of human health and/or the environment; b) generation time in natural ecosystems, sexual and asexual reproductive cycle; c) information on survival, including seasonability and the ability to form survival structures; d) pathogenicity: infectivity, toxigenicity, virulence, allergenicity, carrier (vector) of pathogen, possible vectors, host range including non-target organism. Possible activation of latent viruses (proviruses). Ability to colonise other organisms; e) antibiotic resistance and potential use of these antibiotics in humans and domestic organisms for prophylaxis and therapy; f) involvement in environmental process: primary production, nutrient turnover, decomposition of organic matter, respiration, etc.	No specific recommendation	/

Technical dossier	**GL-MED-GMO WG's guidelines**	
Sections	***Recommendations of the GL-MED-GMO WG***	***Justifications***
A.12. Nature of indigenous vectors a) sequence; b) frequency of mobilisation; c) specificity; d) presence of genes which confer resistance.	No specific recommendation	/
A.13. History of previous genetic modifications.	The applicant may also refer to the history of use of medicinal products containing GMOs of a similar nature to the one concerned by the application (identical vector or parental virus, for example).	The WG considers it necessary to obtain points of comparison regarding the risk of release of the latter (particularly in the context of an application for authorisation of a clinical trial, when no data are yet available regarding the risk of release of the GMO concerned by the application).
B. Characteristics of the vector		
B.1. Nature and source of the vector.	No specific recommendation	/
B.2. Sequence of transposons, vectors and other non-coding genetic segments used to construct the GMO and to make the introduced vector and insert function in the GMO.	No specific recommendation	/
B.3. Frequency of mobilisation of inserted vector and/or genetic transfer capacities and methods of determination.	No specific recommendation	/
B.4. Information on the degree to which the vector is limited to the DNA required to perform the intended function.	No specific recommendation	/
C. Characteristics of the modified organism		

Technical dossier	**GL-MED-GMO WG's guidelines**	
Sections	***Recommendations of the GL-MED-GMO WG***	***Justifications***
C.1. Information relating to the genetic modification: a) methods used for the modification; b) methods used to construct and introduce the insert(s) into the recipient or to delete a sequence; c) description of the insert and/or vector construction; d) purity of the insert from any unknown sequence and information on the degree to which the inserted sequence is limited to the DNA required to perform the intended function; e) methods and criteria used for selection; f) sequence, functional identity and location of the altered/inserted/deleted nucleic acid segment(s) in question, with particular reference to any known harmful sequence.	The applicant should specify whether there has been clonal selection of the GMO contained in the medicinal product.	The WG believes that information on clonal selection is needed for better assessing the identity and stability of the GMO contained in the medicinal product concerned by the application.

Technical dossier	**GL-MED-GMO WG's guidelines**	
Sections	***Recommendations of the GL-MED-GMO WG***	***Justifications***
C.2. Information on the final GMO a) description of genetic trait(s) or phenotypic characteristics and in particular any new traits and characteristics which may be expressed or no longer expressed; b) structure and amount of any vector and/or donor nucleic acid remaining in the final construction of the modified organism; c) stability of the organism in terms of genetic traits; d) rate and level of expression of the new genetic material; method and sensitivity of measurement; e) activity of the expressed protein(s); f) description of identification and detection techniques, including techniques for the identification and detection of the inserted sequence and vector; g) sensitivity, reliability (in quantitative terms) and specificity of detection and identification techniques; h) history of previous releases or uses of the GMO; i) considerations for human health and animal health, as well as plant health: i) toxic or allergenic effects of the GMOs and/or their metabolic products; ii) comparison of the modified organism to the donor, recipient or (where appropriate) parental organism regarding pathogenicity; iii) capacity for colonisation; iv) if the organism is pathogenic to humans who are immunocompetent: - diseases caused and mechanisms of pathogenicity including invasiveness and virulence, - communicability, - infective dose, - host range, possibility of alteration, - possibility of survival outside of human host, - presence of vectors or means of dissemination, - biological stability, - antibiotic-resistance patterns, - allergenicity, - availability of appropriate therapies, v) other product hazards.	The applicant should provide a molecular analysis corresponding to the entire genome and its stability (over a number of passages appropriate to the size of the seed batches, and at least equivalent to the maximum number of passages for the master seed). The applicant should provide a detailed description of any change in the strain's tropism or virulence. Lastly, the applicant should specify the formulation of the medicinal product, particularly in the case of multivalent vaccines, and where appropriate discuss any possible interactions with other strains.	The WG believes it important to provide a molecular analysis of the entire genome, in order to ensure in particular that modifications have not appeared in the viral genome that could alter its biological properties. Sequencing solely at the genetic engineering site would therefore be considered insufficient.

Technical dossier	**GL-MED-GMO WG's guidelines**	
Sections	***Recommendations of the GL-MED-GMO WG***	***Justifications***
III – INFORMATION RELATING TO THE CONDITIONS OF RELEASE AND THE RECEIVING ENVIRONMENT		
A. Information on the release 1. Description of the proposed deliberate release, including the purpose(s) and foreseen products; 2. Foreseen dates of the release and time planning of the experiment, including frequency and duration of releases; 3. Preparation of the site previous to the release; 4. Size of the site; 5. Method(s) to be used for the release; 6. Quantities of GMOs to be released; 7. Disturbance on the site (type and method of cultivation, mining, irrigation or other activities); 8. Worker protection measures taken during the release; 9. Post-release treatment of the site; 10. Techniques foreseen for elimination or inactivation of the GMOs at the end of the experiment; 11. Information on, and results of, previous releases of the GMOs, especially at different scales and in different ecosystems.	The applicant should mention all the clinical trials previously carried out on the medicinal product concerned by the application.	

Technical dossier	GL-MED-GMO WG's guidelines	
Sections	***Recommendations of the GL-MED-GMO WG***	***Justifications***
B. Information on the environment (both on the site and in the wider environment) 1. Geographical location and grid reference of the site(s) (in case of notifications under Part C, the site(s) of release will be the foreseen areas of use of the product); 2. Physical or biological proximity to humans and other significant biota; 3. Proximity to significant biotopes, protected areas or drinking water supplies; 4. Climatic characteristics of the region(s) likely to be affected; 5. Geographical, geological and pedological characteristics; 6. Flora and fauna, including crops, livestock and migratory species; 7. Description of target and non-target ecosystems likely to be affected; 8. A comparison of the natural habitat of the recipient organism with the proposed site(s) of release; 9. Any known planned developments or changes in land use in the region which could influence the environmental impact of the release.	Parallels should be drawn between the breeding or habitat areas of the medicinal product's target and non-target species and the geographical distribution of the parental organism.	
IV. INFORMATION RELATING TO THE INTERACTIONS BETWEEN GMOs AND THE ENVIRONMENT		
A. Characteristics affecting survival, multiplication and dissemination: 1. Biological features which affect survival, multiplication and dispersal; 2. Known or predicted environmental conditions which may affect survival, multiplication and dissemination (wind, water, soil, temperature, pH, etc.); 3. Sensitivity to specific agents.	No specific recommendation	/
B. Interactions with the environment		

Technical dossier	**GL-MED-GMO WG's guidelines**	
Sections	***Recommendations of the GL-MED-GMO WG***	***Justifications***
B.1. Predicted habitat of the GMOs;	Parallels should be drawn between the breeding or habitat areas of the target and non-target species of the medicinal product and the foreseeable distribution of the modified organism.	/
B.2. Studies of the behaviour and characteristics of the GMOs and their ecological impact, carried out in simulated natural environments such as microcosms, growth rooms, greenhouses;	No specific recommendation	
B.3. Genetic transfer capacity: a) post-release transfer of genetic material from GMOs into organisms in affected ecosystems; b) post-release transfer of genetic material from indigenous organisms to the GMOs;	The applicant should take into account firstly the possibility of administering the medicinal product on a multi-species farm, and secondly the possibility of administering multiple medicinal products (particularly regarding vaccines).	The WG considers that the risk of release may be modified in multi-species farming, and that an interaction between strains should be considered in the case of administration of multiple vaccines.
B.4. Likelihood of post-release selection leading to the expression of unexpected and/or undesirable traits in the modified organism;	No specific recommendation	/
B.5. Measures employed to ensure and to verify genetic stability. Description of genetic traits which may prevent or minimise dispersal of genetic material; methods to verify genetic stability;	No specific recommendation	/
B.6. Routes of biological dispersal, known or potential modes of interaction with the disseminating agent, including inhalation, ingestion, surface contact, burrowing, etc.;	No specific recommendation	/
B.7. Description of ecosystems to which the GMOs could be disseminated;	No specific recommendation	/
B.8. Potential for excessive population increase in the environment;	No specific recommendation	/
B.9. Competitive advantage of the GMOs in relation to the unmodified recipient or parental organism(s);	No specific recommendation	/

Technical dossier	**GL-MED-GMO WG's guidelines**	
Sections	***Recommendations of the GL-MED-GMO WG***	***Justifications***
B.10. Identification and description of the target organisms, if applicable;	No specific recommendation	/
B.11. Anticipated mechanism and result of interaction between the released GMOs and the target organism(s), if applicable;	No specific recommendation	/
B.12. Identification and description of non-target organisms which may be adversely affected by the release of the GMO, and the anticipated mechanisms of any identified adverse interaction;	No specific recommendation	/
B.13. Likelihood of post-release shifts in biological interactions or in host range;	No specific recommendation	/
B.14. Known or predicted interactions with non-target organisms in the environment, including competitors, preys, hosts, symbionts, predators, parasites and pathogens;	No specific recommendation	/
B.15. Known or predicted involvement in biogeochemical processes;	No specific recommendation	/
B.16. Other potential interactions with the environment.	No specific recommendation	/
V. INFORMATION ON MONITORING, CONTROL, WASTE TREATMENT AND EMERGENCY RESPONSE PLANS		
A. Monitoring techniques 1. Methods for tracing the GMOs, and for monitoring their effects; 2. Specificity (to identify the GMOs and to distinguish them from the donor, recipient or, where appropriate, the parental organism), sensitivity and reliability of the monitoring techniques; 3. Techniques for detecting transfer of the donated genetic material to other organisms; 4. Duration and frequency of the monitoring.	The applicant should describe the pharmacovigilance associated with the emergence of recombinant strains, and in particular the events that may lead to these strains being sought (such as an increase in the mortality of vaccinated animals, for example).	

Technical dossier	**GL-MED-GMO WG's guidelines**	
Sections	***Recommendations of the GL-MED-GMO WG***	***Justifications***
B. Control of the release 1. Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of release or the designated area for use; 2. Methods and procedures to protect the site from intrusion by unauthorised individuals; 3. Methods and procedures to prevent other organisms from entering the site.	No specific recommendation	/
C. Waste treatment 1. Type of waste generated; 2. Expected amount of waste; 3. Description of treatment envisaged.	It should be specified whether or not the system for disposing of infectious clinical waste (DASRI) is used.	
D. Emergency response plans 1. Methods and procedures for controlling the GMOs in case of unexpected spread; 2. Methods for decontamination of the areas affected, e.g. eradication of the GMOs; 3. Methods for disposal or sanitation of plants, animals, soils, etc. that were exposed during or after the spread; 4. Methods for the isolation of the area affected by the spread; 5. Plans for protecting human health and the environment in case of the occurrence of an undesirable effect.	No specific recommendation	/

ERA	**GL-MED-GMO WG's guidelines**	
Subsection	***Recommendations of the GL-MED-GMO WG***	***Justifications***
ENVIRONMENTAL RISK ASSESSMENT	No specific recommendation – pending publication of an updated "Notice to applicants".	/