Common application form for investigational medicinal products for human use that contain or consist of AAV vectors[1]

Note 1: This application form can be used for submissions in the following jurisdictions: Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Portugal, Romania, Slovenia, Spain and Norway.

Note 2: The application form must be accompanied by the SNIF (summary notification information format for notifications concerning the deliberate release into the environment of genetically modified organisms for purposes other than for placing on the market)[2] in the case of submissions that are made under Directive 2001/18/EC.

Document history	Publication date	Description of main changes
Version 1	October 2019	
Version 2	December 2020	Endorsement by additional Member States (LT, SI)
Version 3	January 2022	Endorsement by an additional Member State (EE) and NO

[1] This document has not been adopted by the European Commission and, therefore, it does not contain the official position of the European Commission.

[2] Council Decision 2002/813/EC establishing, pursuant to Directive 2001/18/EC of the European Parliament and of the Council, the summary notification information format for notifications concerning the deliberate release into the environment of genetically modified organisms for purposes other than for placing on the market (OJ L 280,18.10.2002, p.62).

1. Introduction

Clinical trials conducted in the EU with investigational medicinal products that contain or consist of genetically modified organisms ("GMOs"[3]) must comply with the legislation governing the authorization of clinical trials.[4]

Clinical trials with medicinal products that contain or consist of GMOs must also comply with applicable requirements under Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms[5] ("deliberate release framework") and/or under Directive 2009/41/EC on the contained use of genetically modified micro-organisms ("contained use framework").[6]

This application form implements the requirements of the Directive 2009/41/EC and of the Directive 2001/18/EC, as adapted to the specific characteristics of adeno-associated viral vectors ("AAVs") contained in investigational medicinal products for human use.

This is an application form for investigational medicinal products for human use that contain or consist of AAVs (hereafter referred to as "clinical vectors"). However, if the application concerns an investigational medicinal product that contains or consist of AAVs that has already been granted a marketing authorisation, the *submission form for use in case of clinical trials with authorised medicinal products* should be used (provided that the submission form has been endorsed by the competent authorities in the relevant jurisdiction).

The application form has been endorsed by Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Portugal, Romania, Slovenia, Spain and Norway.

2. Explanatory notes

The common application form is without prejudice to consultation requirements that exist under Directive 2001/18/EC.

In addition, certain national requirements may need to be considered by developers of medicinal products before they submit the application form to the relevant competent authorities:

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[3] Throughout this document, the term "GMO" should be understood as covering both genetically modified organisms as defined under Article 2(2) of Directive 2001/18/EC, and genetically modified micro-organisms within the meaning of Article 2(b) of Directive 2009/41/EC.

[4] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC, (OJ L158, 27.5.2014, p.1). Until the Regulation applies, Directive 2001/20/EC is applicable (Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, OJ L121,1.5.2001, p.34).

[5] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (OJ L 106, 17.4.2001, p. 1).

[6] Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms (OJ L 125, 21.5.2009, p. 75).

Austria:

Applicants should send separate submissions in case there are multiple sites concerned in Austria (including clinical premises, laboratories in which activities with GMOs are carried out, locations of storage of the investigational medicinal product and location of storage of samples from clinical trial subjects that contain GMOs).

Further information is available at:
https://www.sozialministerium.at/site/Gesundheit/Gentechnik/Rechtsvorschriften_in_Oesterreich/

Belgium:

The common application form should be part of a biosafety dossier submitted by each of the clinical sites where the investigational medicinal product will be administered. However, one person (*e.g.* the sponsor) can be empowered by the concerned sites to submit all the necessary notifications, provided that the person responsible for the activity is clearly indicated in the form.

More information on procedural requirements and forms for the three regions is available at: https://www.biosafety.be/content/contained-use-gmos-andor-pathogenic-organisms-notification-procedures.

Czech Republic:

Each clinical site as well as other institutions where the activities with GMOs will take place (*e.g.* laboratories that are not premises of one of the clinical sites) should submit a separate notification for deliberate release or for contained use, as appropriate. However, one person (*e.g.* the sponsor) can be empowered by the concerned sites/institutions to submit all the necessary notifications.

France:

For investigational medicinal products that are assessed under the contained use framework, applicants should send separate submissions in case there are multiple sites concerned in France.

Italy:

For investigational medicinal products that are assessed under the contained use framework, each clinical site (including clinical premises, laboratories in which activities with GMOs are carried out, locations of storage of the investigational medicinal product and location of storage of samples from clinical trial subjects that contain GMOs) should submit a separate notification. However, one person (*e.g.* the sponsor) can be empowered by the concerned sites/institutions to submit all the necessary notifications.

It is stressed that, in case the submission is made by a third party on behalf of the site, the responsibilities of the site holders and users concerned (as set out under Legislative Decree n. 206/2001) remain unchanged.

The Netherlands:

More information on national procedural requirements and forms is available at: https://www.loketgentherapie.nl/en/aav

COMMON APPLICATION FORM FOR INVESTIGATIONAL MEDICINAL PRODUCTS FOR HUMAN USE THAT CONTAIN OR CONSIST OF AAV VECTORs

SECTION 1 – ADMINISTRATIVE INFORMATION

1.1. Identification of the applicant.

Organisation Name:	
Address Details:	
Contact person:	
Telephone No:	
Email Address:	

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:	

1.3 Identification of the manufacturer of the clinical vector.

Organisation Name:	
Manufacturing location:	

SECTION 2 –INFORMATION RELATING TO THE INVESTIGATIONAL MEDICINAL PRODUCT

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.

Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.

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.

Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.

2.3. Provide a diagram ('map') of the clinical vector.

Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.

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.

Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.

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.

Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.

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.

SECTION 3 –INFORMATION RELATING TO THE CLINICAL TRIAL

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:	

3.2. Intended location(s) of the study.

The applicant should provide information about the sites located in the country of submission of the application.

In some jurisdictions, 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.*[7]

- *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).*[8]

- *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).*[9]

Organisation Name:	
Address Details:	
Contact person:	
Telephone No:	
Email Address:	
Planned activities:	
Containment level:	
Name and contact details of the responsible person[10]:	

Organisation Name:	
Address Details:	
Contact person:	
Telephone No:	
Email Address:	
Planned activities:	
Containment level:	
Name and contact details of the responsible	

[7] Information about the location of laboratories is required for applications submitted to Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Portugal and Spain. In case of submissions to these jurisdictions, fill in the relevant table for laboratories that conduct specialised analysis referred in the protocol of the clinical trial only; laboratories that perform standard laboratory diagnostics analysis need not be listed.

[8] This information should be provided for applications submitted to Croatia, Germany, Ireland and Spain. This information should be provided for applications submitted to Belgium, Czech Republic and Finland, unless there is a contained use notification covering the storage of the product.

[9] This information should be provided for applications submitted to Germany and Ireland.

[10] The responsible person is either the person responsible for supervision and safety as provided for under Annex V of Directive 2009/41/EC, or the responsible scientist as provided for under Annex IIIA of Directive 2001/18/EC.

person:	

(Applicant should complete as many tables as necessary)

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.[11]

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.

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	

[11] In case of applications submitted to Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Ireland, Italy, the Netherlands and Spain, 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.

laxatives, administration of a medicinal product that could enhance the replication activity of the clinical vector, administration of a plasmid-based medicinal product):	

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) Recommendations given to clinical trial subjects to prevent dissemination (where applicable).

g) Recommendations on donation of blood/cells/tissues/organs by the clinical trial subject.

(i) Other measures (where applicable).

3.7. Sampling and further analyses of samples from study subjects

This Section should be filled in where samples are being taken from patients which may contain GMOs in the context of the clinical trial and the application is submitted to the following jurisdictions: Croatia, Czech Republic, Germany, Ireland, the Netherlands, Spain

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[12] testing of the samples and indicate whether the clinical vector is generated *de novo* during the testing.

SECTION 4 – OTHER DATA REQUIREMENTS

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 if the application is submitted to the following jurisdictions: Austria, Belgium, Croatia, Czech Republic, Finland, France, Hungary, Ireland and Italy.

[12] Standard clinical care tests as well as tests required to fulfil long-term follow-up of clinical trial subjects need not be mentioned.

4.2 Other information

Submissions to Austria:

In addition to the plan of the site, a description of the location of the autoclave should be provided –as appropriate- as part of the description of the measures to prevent dissemination into the environment referred in Section 3.6 (d) and (e).

Submissions to Belgium:

In addition to the plan of the site, a description of the location of the autoclave and the biosafety cabinet should be provided –as appropriate- as part of the description of the measures to prevent dissemination into the environment referred in Section 3.6 (d) and (e).

The applicant is also asked to provide an overview (table) of the rooms involved in the CT activity by indicating for each of those the number of the room, the type of handling carried out (e.g. storage, administration of the IMP, reconstitution of the IMP) and the containment level.

Submissions to Czech Republic:

In addition to the plan of the site, a description of the location of the autoclave should be provided –as appropriate- as part of the description of the measures to prevent dissemination into the environment referred in Section 3.6 (d) and (e).

Submissions to Denmark:

- *The applicant should explain if left-overs are stored at the clinical site and, if in the affirmative, for how long as part of the information submitted in Section 3(6)(d).*
- *The applicant should provide the following information on waste treatment in Section 3(6)(e):*
  - *Whether and for how long the waste will be stored (or frequency of waste disposal),*
  - *Storage location,*
  - *Logistics for on-site transportation of the waste (similar as asked for the clinical vector in Section 3.4), and*
  - *In case of chemical decontamination whether the chosen disinfectant and method is sufficiently active against the clinical vector (similar as in Section 3.6.c)*

Submissions to France:

The plan of the site should indicate clearly the location of a PSMII, or an equivalent device.

Submissions to Germany:

- *The applicant is not required to provide further information in Section 3(6)(c) if he/she confirms that the disinfectant and decontamination procedure are included in the list of the Robert Koch Institute of currently approved disinfectants and disinfectant procedures or the VAH (Verbund für Angewandte Hygiene e.V) list of disinfectants.*
- *The applicant should explain if left-overs are stored at the clinical site and, if in the affirmative, for how long as part of the information submitted in Section 3(6)(d).*

- *The applicant should provide the following information on waste treatment in Section 3(6)(e):*
  - *Whether and for how long the waste will be stored (or frequency of waste disposal),*
  - *Storage location,*
  - *Logistics for on-site transportation of the waste (similar as asked for the clinical vector in Section 3.4), and*
  - *In case of chemical decontamination whether the chosen disinfectant and method is sufficiently active against the clinical vector (similar as in Section 3.6.c)*
- *If samples are stored at the clinical site, the maximum duration of the storage should be stated in Section 3.7 (c).*
- *The applicants is required to provide emergency response plans.*

Submissions to Ireland:

- *In addition to the plan of the site, a description of the location of the autoclave should be provided –as appropriate- as part of the description of the measures to prevent dissemination into the environment referred in Section 3.6 (d) and (e).*
- *If samples are stored at the clinical site, the maximum duration of the storage should be stated in Section 3.7(c).*

Submissions to Italy:

- *In addition to the plan of the site, a description of the location of the autoclave should be provided –as appropriate- as part of the description of the measures to prevent dissemination into the environment referred in Section 3.6 (d) and (e).*
- *If the manufacturer of the clinical vector is located in Italy, the authorisation issued to the premises should be declared in Section 1.3.*

SECTION 5- ENVIRONMENTAL RISK ASSESSMENT

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 ☐

If the answer to the above is NO, the following information should be provided:

- *For submissions made under Directive 2001/18/EC*: an environmental risk assessment is required in accordance with Annex II thereof.

- *For submissions made under Directive 2009/41/EC*: an assessment of the risks to human health and the environment in accordance with Article 4 thereof.