Common Application form for clinical research with human cells genetically modified [1]

NOTE 1: This application form can only be used for:

- **human cells genetically modified by means of retro/lentiviral vectors, including genome edited cells, in cases where the applicant demonstrates that:**
  (1) there is no risk of formation of replication competent virus, and
  (2) residual infectious retro/lentiviral vector particles have been reduced to negligible concentrations in the finished product, or there is negligible risk associated with the presence of residual infectious viral vector particles in the finished product;

- **human cells genetically modified by means of adeno-associated viral vectors, including genome edited cells, in cases where the applicant demonstrates that there is no risk of formation of replication competent virus; and**

- **human cells genetically modified without viral vectors, including genome edited cells.[2]**

NOTE 2: This application form can be used for submissions in the following jurisdictions:
Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy*, Latvia, Lithuania, Luxembourg, the Netherlands, Portugal, Romania, Spain, Sweden, and Norway.**

NOTE 3: 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)[3] in the case of submissions that are made under Directive 2001/18/EC.

Document history	Publication Date	Description of main changes
Version 1	July 2018	
Version 2	December 2018	Endorsement by additional Member States (EE, FI, IE, SE)
Version 3	October 2019	Endorsement by additional Member States (CZ, LV, NL). Presentation of confidential information (to be submitted in an Annex.)
Version 4*	December 2020	Adaptation of requirements regarding absence/residual presence of infectious viral vector particles in the finished product (for human cells modified by means of retro/lentiviral vectors) and inclusion of requirements for human cells modified by means of AAVs. Endorsement by additional Member States (HR, LT, SI). Update of additional national requirements.
Version 5**	November 2021	Inclusion of human cells genetically modified without viral vectors and genome edited cells.

[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] The common application should be used when the genetically modified cells are considered GMOs. Reference is made to the document on frequently asked questions "Medicinal products for human use containing or consisting of GMOS: interplay between the EU legislation on medicinal products and GMOs".
[3] 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)
* Version 4 has not been endorsed by Cyprus and Malta.
** Version 5 has not been endorsed by Malta and Slovenia.
*** In Italy, this common application form has been endorsed by the competent authorities responsible for the implementation of the Directive 2009/41/EC on the contained use of genetically modified micro-organisms only.

COMMON APPLICATION FORM FOR CLINICAL RESEARCH WITH HUMAN CELLS GENETICALLY MODIFIED [4]

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. Information about the clinical trial[5]:

a) General information about the clinical trial:

EudraCT-number (where available):	
Deliberate release reference number (where available and	

[4] Throughout this document, the term human cells genetically modified should be understood as including also genome edited cells.

[5] For applications submitted in Sweden -where a single procedure has been put in place for submission of the clinical trial and GMO application- only the Eudra CT-number is mandatory.

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, please identify the countries concerned:	

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,[6] the location(s) of laboratories[7] 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).

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

[6] The location of the site(s) where donation, procurement and testing of the donor cells take place need not be listed.

[7] Laboratories that perform routine laboratory diagnostics analysis need not be listed.

the responsible person[8]:	

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

(Applicant should complete as many tables as necessary)

c) Logistics for transportation:

The applicant should provide information about the logistics for in-house transportation.

SECTION 2 –INFORMATION ABOUT THE INVESTIGATIONAL MEDICINAL PRODUCT

2.1 Characterisation of the finished investigational medicinal product.

a) General information:

Description of the finished medicinal product	Autologous ☐ Allogeneic ☐
	Specify type of cells (*e.g*. hematopoietic stem cells…): ……
	Viral vector used: Retrovirus ☐

[8] 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.

	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:	

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.

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 confidentiality is claimed, a summary that can be made public should be provided in this section.

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.

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 confidentiality is claimed, a summary that can be made public should be provided in this section.

(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.

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 confidentiality is claimed, a summary that can be made public should be provided in this section.

2.2. Molecular characterisation of the applied vectors.

This section should not be filled in case of human cells genetically modified without a viral vector.

a) Map of the construct:

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 confidentiality is claimed, a summary that can be made public should be provided in this section.

b) Description of each of the components of the vector:

The applicant should provide a detailed description of each of the components of the vector used.

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 confidentiality is claimed, a summary that can be made public should be provided in this section.

SECTION 3- CONTROL MEASURES

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).

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.

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:	

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.

Identified risk(s)	**Risk minimisation measure(s)**

SECTION 4- ENVIRONMENTAL RISK ASSESSMENT

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 ☐

If the answer to any of 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.

SECTION 5 - MANUFACTURE OF THE INVESTIGATIONAL MEDICINAL PRODUCT

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:	

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.

Please note that the possibility to request for (simultaneous) authorisation for manufacturing activities and for the conduct of the clinical trial by means of this application form is only available in Czech Republic, Greece, Hungary, and Romania. For submissions outside these jurisdictions Section 5.2 should not be filled in.

a) Administrative information about the site:

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

b) Description of manufacturing operations and risk minimisation measures:

Information about the vector production system:

b.1. 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 ☐

b.2. Cells from HIV/HTLV positive donors are excluded (relevant for human cells genetically modified by means of retro/lentiviral vectors):

Yes ☐

No ☐

b.3. 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.

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 confidentiality is claimed, a summary that can be made public should be provided in this section.

b.4. 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

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 confidentiality is claimed, a summary that can be made

public should be provided in this section.

Risk minimisation measures

c) Level of containment:

SECTION 6- OTHER DATA REQUIREMENTS

6.1. Plan of the site(s) concerned:

Applicant 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, Czech Republic, Finland, France, Hungary, Ireland, Italy, Portugal or Norway.

Applicant should provide a copy of the plan of site where manufacturing activities take place (if the application covers manufacturing activities, i.e. Section 5.2) in case the application is intended for Czech Republic, Italy or Hungary.

6.2 Other information:

For submissions to Austria:

Applicants should also provide:

- *a map of the laboratories and room in which activities with the GMO are carried out under the terms of this application,*
- *the location of the autoclave, and*
- *the name of members of the biosafety committee (Kommittee für die biologische Sicherheit) and curriculum vitae thereof.*

For submissions to Belgium:

In addition to the description of measures to prevent risk of accidental transfer (section 3.1), the applicant should provide, on a map of the room, the location of relevant biosafety devices (e.g. biosafety cabinet, centrifuge, non-manually operated sink should be indicated) whenever used during preparation of the medicinal product prior administration.

In addition to the description of the measures to prevent dissemination into the environment (section 3.3), the applicant should provide:

-a description of the location of the autoclave and the intermediate waste storage room, as appropriate.

- an estimation of the volume of waste generated per month and the frequency of waste removal by a waste collection firm. The name of the firm must be mentioned.

- information on the validation of the proposed waste inactivation procedures and/or disinfection procedures (e.g. scientific literature, manufacturer's instructions or in house validation of the method).

For submissions to Germany:

The applicant should provide information about the conditions of storage (including restrictions of access) and the maximal storage duration of the IMP at the clinical site.

The applicant is asked to confirm that the disinfectant and decontamination procedure used (e.g. for elimination or inactivation of left-overs, decontamination of potentially contaminated materials, surfaces, and areas after IMP administration or after accidental spilling of the IMP) are include 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 provide information on the personal protective equipment of the health care professionals during sampling and during decontamination of potentially contaminated surfaces and areas, and during decontamination and disposal of left-overs and waste.

If left-overs, waste, or samples of the subjects are stored at the clinical site for more than 3 days, the applicant is asked to provide information about the condition of storage and the maximal storage duration.

The applicant should provide information about the logistic for in-house transportation of left-overs, waste, or samples of the subjects.

For submissions to Ireland:

The applicant should provide information on the type and extent of GM contaminated waste generated and how the waste will be collected, stored and inactivated including where applicable off-site treatment. The application should also provide disinfection and decontamination procedures including -where applicable- details of validation, details of where the medicinal product will be prepared prior to administration, types of PPE that will be worn.

***For submissions to Italy**:*

The applicant should provide the following additional information:

- *In Section 1: In addition to an standard Email address, a certified Email address should be provided for subsections 1.1., 1.2 and 1.3. Additionally, in Section 1.3,* where the EudraCT-*number is not available, references to the application for authorisation of the clinical trial sent to the Italian Medicines Agency (AIFA) should be provided.*

- *In Section 3.3: The name and the licence code of the firm authorized to treat wastes has to be provided.*

- *In Section 5.2: Permit for production and clinical research contained use can be asked at the same time, using two different forms. For production it is recommended to use the national form, available at:*
  http://www.salute.gov.it/portale/ministro/p4_8_0.jsp?lingua=italiano&label=servizionline&idMat=BIOT&idAmb=NIA&idSrv=A1&flag=P#moduli

- *Additional information: The applicant should provide the national code reported on the authorization issued to the clinical premise. If variations to the installation occurred, they have to be notified using the national form available at:*
  http://www.salute.gov.it/portale/ministro/p4_8_0.jsp?lingua=italiano&label=servizionline&idMat=BIOT&idAmb=NIA&idSrv=A1&flag=P#moduli(salute.gov.it).

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

  The applicant should provide in a separate document, a map indicating the rooms in which the investigational medicinal product is administered and the patients' recovery rooms. The map is expected to be identical to the one submitted with the clinical premise notification.
  The applicant should, in addition to the plan of the clinical site, provide information on the location of the autoclave used for waste inactivation and treatment, highlighting it on the plan of the clinical 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 (section 3.3).
  Signatures of both user and employer are required.

For submissions to the Netherlands:

In the Netherlands, the scope of a permit does not have to be limited to one clinical trial. It is possible to broaden the scope of a permit, e.g. to cover the whole clinical development program of a GMO.

Only legal entities where the trial is performed can act as the permit holder, i.e. the institution/hospital. Sponsors are encouraged to contact the environmental safety officer(s) of the institution/hospital where the work is to be performed. The environmental safety officer has knowledge on the procedures in the Netherlands and can be of assistance in the application procedure.

A submission should be accompanied by documentation required for legal and administration purposes (e.g. general personal information on the responsible employee and the environmental safety officer has to be submitted in a separate document for compliance to the provisions of the General Data Protection Regulation (EU)2016/679). The required documents are available on the website (see below).

Sampling and processing of samples is part of the scope of a GMO-permit in the Netherlands, and is therefore to be included in section 3.
Information on RCL testing can be waived in the Netherlands for certain SIN LVV production systems.

More information on national procedural requirements and forms is available at:

https://www.loketgentherapie.nl/en/gm-cells

***For submissions to Romania that cover manufacturing activities**:*

The applicant should provide the GNSS (global navigation satellite system) coordinates of the site(s) where the concerned manufacturing activities take place.

For submissions to Spain:

The applicant shall put in place appropriate biosafety measures during in house transport, storage, handling and administration of the investigational medicinal product as well as during in house transport and handling of samples from clinical trials subjects that may contain GMOs. The applicant shall detail in the relevant sections of the application form the measures implemented and shall ensure that all sites that take part in the clinical trial implement those measures.

More information on national procedural requirements and forms (in Spanish language) is available at: https://www.miteco.gob.es/es/calidad-y-evaluacion-ambiental/temas/biotecnologia/organismos-modificados-geneticamente-omg-/notificaciones-y-autorizaciones/proc_autorizacion.aspx