National guidance document for the common application form for clinical research with human cells genetically modified by means of retro/lentiviral vectors

Introduction

In order to facilitate a streamlined application of studies using genetically modified human cells in Europe, a good practice document on the assessment of GMO related aspects in the context of clinical trials with human cells genetically modified by means of retro/lentiviral vectors has been developed by EU national competent authorities and the Commission services ("*Good Practice on the assessment of GMO-related aspects in the context of clinical trials with human cells genetically modified by means of retro/lentiviral vectors*", hereafter referred to as "good practice document")[1]. The good practice document is accompanied by a common application form for GMO aspects that should be used for applications of studies using human cells genetically modified by means of retro/lentiviral vectors.

Guidance document

The Netherlands competent authority has drafted a guidance document that clarifies the information requirements to facilitate a swift handling of GMO applications using human cells genetically modified by means of retro/lentiviral vectors. The purpose of this guidance document is to provide additional information regarding national requirements as required for submission in the Netherlands. This guidance document contains information on the documents required for submission to the Netherlands, confidentiality, the scope of a permit application in the Netherlands and particular information requirements with respect to the information requested in the common application form. The information requirements requested in the common application form are drafted in alignment with The Netherlands Commission on Genetic Modification (COGEM).

The answers in the common application form should demonstrate that the good practice document is applicable to the proposed work. In addition to the common application form the following appendices (among others for legal and administrative requirements) should be accompanying your application:

- General (personal) information
- Consent form
- SNIF B Form

Confidentiality

The common application form requests the information needed for the Ministry of Infrastructure and Water Management (IenW) to grant the necessary permit. All information provided in this form and the accompanying documentation constitutes part of the decision to be made and for this reason is in principle publicly accessible; the information will also be accessible to the public during and after the procedure.

The applicant may ask for parts of the information provided to be kept confidential. In that case, the applicant must substantiate why the information is of a confidential nature as well as a convincing explanation that the lifting of confidentiality will adversely affect the applicant's competitive position.

[1] https://ec.europa.eu/health/human-use/advanced-therapies_en

A publicly available summary of confidential information must be given, containing the information needed for a clear general understanding of the application and in order to assess whether the good practice document is applicable and to draft the permit. Confidential information must be included in a separate annex marked as 'confidential'.

Applicants are urged to limit the amount of confidential information. The information requirements are drafted as such that in most cases confidential information is not needed.

Scope of permit applications in the Netherlands

An application does not need to be limited to a specific clinical protocol that the applicant wishes to perform. If there are no consequences for the risk analysis, the application can be drawn up with a wider scope, for instance as for a larger number of patients. If desired, the whole clinical development program can be covered by a single permit, where it is important that the activities of the full clinical development program that will be performed fall under the scope of the application and accompanying environmentalrisk assessment. Before submitting an application with a wider scope, you are advised to contact the GMO office for an informal discussion on the matter.

Specific guidance on the common application form

SECTION 1 – ADMINISTRATIVE INFORMATION

Section 1.1 (Identification of the applicant). Contains information about the legal entity (i.e. the hospital or site where the proposed work will be performed). Only fill in "Organisation Name" and "Address Details". All other fields should be left empty as this information is already part of the non-public annex "General (personal) information".

Section 1.2 (Identification of the sponsor, to the extent that is different from the applicant). Should be left empty as this information is not required for the national procedure in the Netherlands.

Section 1.3.a (Information about the clinical trial - General information about the clinical trial). Include a first sentence in the field "Objective of the study" the title of the application, followed by the description of the objection of the study.

Section 1.3b (Information about the clinical trial – Intended location(s) of the study). Only fill in "Organisation Name" and "Address Details". The other fields should not be filled in. Applicants should send separate submissions in case there are multiple sites concerned in the Netherlands (including clinical premises, laboratories in which activities with GMO's are carried out, locations of storage of the investigational medicinal product and location of storage and/or processing of samples from clinical trial subjects that contain GMOs).

Section 1.3c (Information about the clinical trial – Logistics for transportation). A description that "*In-house transport takes place in a closed, break-proof, leak-proof packaging.*" will suffice.

SECTION 2 –INFORMATION RELATING TO THE INVESTIGATIONAL MEDICINAL PRODUCT

Section 2.1a (Characterisation of the finished investigational medicinal product – General information). Specify the cell type, also indicate if other modifications have been made to the cells by for instance the use of plasmid DNA or site-directed nucleases. If this is the case the good practice document should be supplemented with a risk assessment that covers those particular aspects not covered in the good practice document.

Section 2.1b (Characterisation of the finished investigational medicinal product – Absence of replication competent virus particles in the finished product). In accordance with the COGEM advice CGM/190729-01, information regarding the performed RCL test need not to be supplied for third generation SIN lentiviral systems when the application does not include HIV-positive patients or donors. In this case only data (plasmid maps or a description of the components present on the transfer plasmid, packaging plasmids and pseudotyping plasmids) must be supplied (see 2.2.b) demonstrating the use of a third generation SIN lentiviral system (see Article 2 of the GMO Regulation for definitions). In accordance with the COGEM advice CGM/190729-01, a third-generation SIN lentiviral system with a pseudotyping envelope protein other than the *Vesicular Stomatitis Virus* envelop protein can also be used without the need for supplying information regarding the performed RCL test.

Information regarding the performed RCL test must be supplied for all other lentiviral systems. In this case, a brief description of the test(s) used, including the detection limit, and the acceptance criteria, must be provided. Furthermore, is should be confirmed that the test is validated.

Information regarding the performed RCR test must be supplied for retroviral systems. In this case, a brief description of the test(s) used, including the detection limit, and the acceptance criteria, must be provided. Furthermore, is should be confirmed that the test is validated.

Section 2.1c (Characterisation of the finished investigational medicinal product – Absence of residual infectious viral vector particles in the transduced cells). Preferably, experimental data should be provided that demonstrates that the transduced cell product does not contain any residual viral particles. In this case, a brief description of the test(s) used, including the detection limit, and the acceptance criteria, must be provided. Furthermore, is should be confirmed that the test is validated.

If no experimental data are available, a theoretical assumption can be provided substantiating that the transduced cell product does not contain any residual viral particles. For this purpose the COGEM formula as described in the good practice document can be applied. In case the COGEM formula is used, a minimal reduction ratio of 100 is required.

In case the presence of residual infectious viral particles cannot be excluded the good practice document must be supplemented with a risk assessment that covers the risks of free viral particles since these aspects are not covered in the good practice document.

Section 2.2a (Molecular characterisation of the applied vectors – Map of the construct). A description of the vector genome (LTRs and intermediate components) must be provided. The function and origin of the intermediate components must be described briefly. *Example: the vector genome consist of a chimeric 5'LTR (human cytomegalovirus promoter and HIV-1 5'LTR U5 and R regions), HIV-1 primer binding site, packaging signal (including a truncated gag), Rev responsive element and central polypurine tract, a promoter of human origin, an intron of mammalian origin, an anti-CD19 chimeric antigen receptor (consisting of anti CD19 binding domain, a hinge, a transmembrane and costimulatory domains) of mammalian origin, a woodchuck hepatitis virus posttranscriptional*

regulatory element, a HIV-1 SIN 3'LTR. Followed by a brief description of the function of these components.

In addition, it must be confirmed that the identity of the vector genome (LTRs and intermediate components) has been verified by sequencing.

Section 2.2b (Molecular characterisation of the applied vectors – Description of each of the components of the vector:).

For lentiviral systems, a description of the lentiviral system must be supplied (plasmid maps or a description of the components present on the transfer plasmid, packaging plasmid(s) and pseudotyping plasmid and production cell line). *Example: for a description of the vector genome on the transfer plasmid see 2.2a. Two packaging plasmids are used, one expressing HIV-1 Rev, one expressing HIV-1 gag/pol. The pseudotyping plasmid expresses a gibbon ape leukemia virus envelop protein.* It must be confirmed that the production cells used for production of the lentiviral vector are free of HIV-1, HIV-2, HTLV-1, HTLV-2, SIV and other relevant retro/lentiviruses that may result in complementation of, or recombination with, the lentiviral vector used.

For retroviral systems, a description of the retroviral system must be provided (plasmid maps or a description of the components present on the transfer plasmid, packaging plasmid(s) and pseudotyping plasmid or in the packaging cell line). It must be confirmed that the production cells used for production of the retroviral vector are free of HIV-1, HIV-2, HTLV-1, HTLV-2, SIV and other relevant retro/lentiviruses that may result in complementation of, or recombination with, the retroviral vector used.

SECTION 3 – CONTROL MEASURES

Section 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). A description that "*Standard hospital hygienic measures will be effective during handling and administration of the GMO. In-house transport takes place in a closed, break-proof, leak-proof packaging. Standard hospital hygienic measures will be effective during sampling and further analyses. Samples will be stored in a closed container at the facility under circumstances with restricted access."* will suffice.

Section 3.3 (Measures to prevent dissemination into the environment - Decontamination/cleaning measures after administration). A description that "*Appropriate validated disinfection detergents and methods will be used for decontamination and disinfection."* will suffice.

Section 3.3 (Measures to prevent dissemination into the environment - Elimination or inactivation of left-overs of the finished product at the end of the clinical trial). A description that "*All left-overs of the product will be disposed of as specific hospital waste (UN 3291)."* will suffice.

Section 3.3 (Measures to prevent dissemination into the environment - Waste treatment). A description that "*All disposable waste that has been in contact with the GMO during preparation and administration will be disposed of as specific hospital waste (UN 3291). Non-disposable materials are*

desinfected with appropriate validated disinfection detergents or autoclaved. Waste from sampling and sample processing is disposed of as specific hospital waste (UN 3291).” will suffice.

Section 3.4 (Other risk minimisation measures). It must be stated whether donors/patients are free from HIV-1 and HIV-2 infections. If HIV-positive donors/patients are included, this aspect should be taken into account when answering questions 2.1.b and 2.1.c.

SECTION 5 – MANUFACTURE OF THE INVESTIGATIONAL MEDICINAL PRODUCT

Section 5.1 (Manufacturing site) should be left empty as this information is not required for the national procedure in the Netherlands.