National guidance document for applications for clinical research with human cells genetically modified by means of retro/lentiviral vectors conform article 39b of the Regeling ggo[1]

Introduction

In the Netherlands a dedicated simplified procedure has been set up for clinical research with human cells genetically modified using viral vectors derived from murine gamma retrovirus or human immunodeficiency virus, where there is no risk of formation of replication competent virus, and the medicinal product is free of infectious viral vector particles that are capable of being released in the environment. An application under this simplified procedure (permit subject to fixed conditions ; vergunning onder vaste voorschriften; VoV) can be filed if the proposed work meets certain prespecified criteria and the prespecified environmental risk assessment (ERA).

Note: applications that do not fulfil the criteria to fit the scope of article 39b or that do not meet the prespecified fixed criteria and ERA can be filed using the standard procedure or (if applicable) another simplified procedure.

Note: The environmental safety officer has knowledge on the procedures in the Netherlands and can be of assistance in the application procedure. Contact the environmental safety officer of your institute/hospital for assistance.

Guidance document - VoV

To expedite efficient processing of applications for clinical research with human cells genetically modified using viral vectors derived from murine gamma retrovirus or human immunodeficiency virus, where there is no risk of formation of replication competent virus, and the medicinal product is free of infectious viral vector particles that are capable of being released in the environment where the proposed work is conform article 39b of the Regeling ggo, the Dutch competent authority has drafted a guidance document that clarifies the information requirements to facilitate a swift handling of these GMO applications. The purpose of this document is to clarify requirements for submission in the Netherlands. This guidance document contains (1) information on the documents required for submission in the Netherlands, confidentiality, the scope of a permit application in the Netherlands and (2) clarification of the information requirements with respect to the information requested in the common application form in order to expedite an efficient processing of the application by the Dutch authorities. 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 VoV-application form should demonstrate that the proposed work is conform the prespecified criteria and the prespecified environmental risk assessment. In addition to the VoV-application form the following appendices (among others for legal and administrative requirements) should be accompanying your application:

- SNIF B Form
- General (personal) information

[1] Regeling genetisch gemodificeerde organismen milieubeheer 2013

To guarantee compliance with the General Data Protection Regulation (EC) 2016/679 (GDPR) data related to individuals, such as contact persons or environmental safety officers, need to be submitted in a form for general (personal) information which will be kept confidential.

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. 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 environmental risk 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 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). Do not fill in the name of the principal investigator.

Section 1.3b (Information about the clinical trial – Intended location(s) of the study). Only fill in "Organisation Name" and "Address Details" of the location(s) where the work will be performed under responsibility of the applicant. 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). This section is already filled in conform the prespecified criteria that are a prerequisite for the simplified VoV procedure.

SECTION 2 –INFORMATION RELATING TO THE INVESTIGATIONAL MEDICINAL PRODUCT

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. 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).

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 formula as described in the good practice document can be applied. In case theoretical assumptions are used, a minimal reduction ratio of 100 is sufficient for applications using retroviral vectors and a minimal reduction ratio of 1 is sufficient for applications using lentiviral vectors (conform COGEM advice CGM/190729-01 and CGM/161130-01). Note that the applicant should justify the parameters used in the theoretical argumentation.

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.

Furthermore, 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:).

Depending on the production system used, there are different requirements with respect to RCL-testing (see section 2.1b). Therefore, it is required to include in your application a description of the production system that is used.

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 VSV-G envelop protein.*

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).

SECTION 3 – CONTROL MEASURES

Note: sampling as well as handling, storage, transport and waste treatment of samples is included in this section, as this is part of the scope of a GMO-permit in the Netherlands.

Section 3. These sections are already filled in conform the prespecified criteria that are a prerequisite for the simplified VoV procedure.