**National guidance document for applications for clinical research with human cells genetically modified by means of AAV vectors conform article 39d of the Regeling ggo[[1]](#footnote-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 Adeno-associated dependoparvovirus A or B without harmful inserted sequences. 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 39d 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 39d 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

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).** A general description of the test method(s) used for detection of vector-derived replication-competent virus, detection limit and the acceptance criteria is sufficient. Furthermore, is should be confirmed that the test is validated.

In case a helper virus is used during production of the AAV vector:

Describe the non-modified (wild type) helper viruses or genetically modified (GM) helper viruses in case these have been used in production. It should be confirmed that these helper viruses are removed from the medical product. *Note: In case of a GM-helper virus, a global description (insertions and deletions) of the virus and it’s production should be provided. In addition, the method(s) used to remove the GM helper virus(es) during production must be described and a description of the test(s) used to confirm the absence of the GM helper virus(es), including 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 – Presence of residual infectious viral vector particles in the transduced cells).** N/A

**Section 2.2a (Molecular characterisation of the applied vectors – Map of the construct).** A description of the vector genome (ITRs and intermediate components) must be provided. The function and origin of the intermediate components must be described briefly. *Example: elements present on the AAV clinical vector: 5’ITR of AAV2, human liver-specific promoter, human enhancer, mammalian intron, non-harmful transgene (specify) of human origin, human polyadenylation signal, 3’ITR of AAV2.* Followed by a brief description of the function of the components in the expression cassette. Include a brief description of the physiological function of the transgene and the possible effect of the transgene in individuals other than the patient. From this description it must be clear that no harmful gene product is applied.

Furthermore, it must be confirmed that the identity of the vector genome (ITRs 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:**).

Provide a description of the AAV production system (plasmid maps or a description of the components present on the transfer and packaging plasmid(s) or in the packaging cell line). A global description of the components is sufficient, where it is important that all relevant components (including their origin and function) are shown and/or described. *Example: for a description of the transfer plasmid see 2.2.a. Indicate relevant AAV helper sequences, e.g. rep and cap (provide origin and if applicable modifications in the cap sequence used). Indicate relevant helper sequences, e.g. specify the used adenovirus helper sequences*.

### 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****.** This section is already filled in conform the prespecified criteria that are a prerequisite for the simplified VoV procedure.

1. Regeling genetisch gemodificeerde organismen milieubeheer 2013 [↑](#footnote-ref-1)