National guidance document for the common application form for investigational medicinal products for human use that contain or consist of AAV vectors

Introduction

In order to facilitate a streamlined application of studies using AAV clinical vectors in Europe, a good practice document on the assessment of GMO related aspects in the context of clinical trials with AAV clinical 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 AAV clinical 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 AAV clinical 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 AAV clinical 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 in 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. A publicly available summary of confidential information must be given, containing the information

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

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 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 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 (Identification of the manufacturer of the clinical vector). Should be left empty as this information is not required for the national procedure in the Netherlands.

SECTION 2 –INFORMATION RELATING TO THE INVESTIGATIONAL MEDICINAL PRODUCT

Section 2.1 (Description of the production system). The description of the AAV production system should be based on plasmid maps of the transfer and packaging plasmids. Alternatively, the various components on the plasmids or components present in the production cell line can be described textually. 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: elements present on the AAV clinical vector: 5'ITR of AAV2, human liver-specific promoter, human enhancer, mammalian intron, non-harmful transgene of human origin, human polyadenylation signal, 3'ITR of AAV2. Relevant AAV helper sequences, e.g. rep and cap (provide origin and if applicable modifications in the cap sequence used). Relevant helper sequences, e.g. specify the used adenovirus helper sequences. Followed by a brief description of the function of the components in the expression cassette.*

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

Section 2.3 (Provide a diagram ('map') of the clinical vector). A diagram showing the ITRs and intermediate components or a textual description of the clinical vector that provides similar information *(example: see section 2.1)* must be provided. Provide a brief description of the function and origin of the intermediate components. Note: the answer to this question may also refer to section 2.1 if the information is provided in that section.

Section 2.4 (Molecular characterisation of the clinical vector). It must be confirmed that the identity of the vector genome (ITRs and intermediate components) has been verified by sequencing.

Section 2.5 (Description of the insert). Provide 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.

Section 2.6 (Biodistribution and shedding). Provide a brief description of known data with regard to biodistribution and shedding (reference to source is not required).

SECTION 3 –INFORMATION RELATING TO THE CLINICAL TRIAL

Section 3.1 (General information about the clinical trial). Do not fill in the name of the principal investigator

Section 3.2 (Intended location(s) of the study). Only fill in "Organisation Name" and "Address Details". The other fields should not be filled in. 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 3.3 (Storage of the clinical vector at the clinical site). A description that "*The clinical vector will be stored in a closed container at the facility under circumstances with restricted access."* will suffice.

Section 3.4 (Logistics for on-site transportation of the clinical vector). A description that "*In-house transport takes place in a closed, break-proof, leak-proof packaging.*" will suffice.

Section 3.6a (Measures to prevent dissemination into the environment - Control measures during reconstitution (if applicable), handling and administration). A description that "*Standard*

hospital hygienic measures will be effective during reconstitution, handling and administration of the GMO." will suffice.

Section 3.6b (Measures to prevent dissemination into the environment - Personal protective equipment). A description that "*Medical personnel will follow standard hospital hygienic measures."* will suffice.

Section 3.6c (Measures to prevent dissemination into the environment - Decontamination/cleaning measures after administration or in the case of accidental spilling). A description that "*Appropriate validated disinfection detergents and methods will be used for decontamination and disinfection."* will suffice.

Section 3.6d (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 3.6e (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 3.7a (Sampling and further analyses of samples from study subjects - Describe how samples will be handled/stored/transported). A description that "*Standard hospital hygienic measures will be effective during sampling and further analyses. In-house transport takes place in a closed, break-proof, leak-proof packaging*. *Samples will be stored in a closed container at the facility under circumstances with restricted access*." will suffice.

Section 3.7b (Sampling and further analyses of samples from study subjects - Indicate whether and at which time points samples that may contain the administered clinical vector are taken from study subjects). A description of the range of the sampling time will suffice. (*example: samples will be taken during the 3 years after administering the AAV clinical vector.)*

Section 3.7c (Sampling and further analyses of samples from study subjects - If samples are stored at the clinical site, describe storage location and storage conditions). A description that "*Samples will be stored in a closed container at the facility under circumstances with restricted access".* will suffice. If samples are further analyzed under a contained use license, this can also be indicated.