Guidance document for the common application form for investigational medicinal products for human use that contain or consist of viral vectors

Introduction

In order to facilitate a streamlined application of studies using clinical viral vectors in Europe, a common application form has been developed for GMO aspects that should be used for applications of clinical studies using viral 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 for clinical viral vectors. The purpose of this document is to provide additional guidance regarding national information requirements as demanded for submissions in the Netherlands. This guidance document contains information concerning the documents being part of the application package 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).

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 in combination with the accompanying documentation constitutes part of the ultimate decision 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 the confidentiality will adversely affect the applicant's competitive position. In order to draft the permit, a publicly available summary of the confidential information must be given, containing the information needed for a clear and general understanding of the application. Confidential information must be included in a separate annex marked as 'confidential'.

Applicants are urged to limit the amount of confidential information.

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.

Guidance document

The purpose of this guidance document is to provide additional information regarding national requirements as required for submission in the Netherlands. In the following sections an explanation is given to further specify the information that is or is not required for the national procedure in the Netherlands.

Due to the wide scope of this form, only general guidelines are given and in specific cases other information may be required for adequate substantiation of the environmental risk assessment. Applicants are therefore encouraged to contact the GMO office prior to submission in case of doubt.

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 2.4 (Zoonotic potential of the parental virus). This section should be filled in both for replication competent as well as replication incompetent clinical viral vectors.

Section 2.6: (Pathogenic properties of the parental virus). This section should also include pathogenic properties for non-human hosts, if applicable.

Section 2.10 (Provide a brief description of the manufacturing process of the clinical vector). The description of the manufacturing process should focus on the generation and culturing of the viral vector. A description of the plasmids, viruses and/or cell lines used must be supplied. Include information on overlapping sequences conform the common application form. Plasmid maps or a description of the components present on the plasmids should be provided for all plasmids (e.g transfer, packaging, helper and/or plasmids). Describe any genetically modified (GM) or wild type

(helper) virus used during the production process. Information regarding the cell lines used should be provided in section 2.11.

Section 2.12 (Contaminating replication-competent virus). A general description of the test method(s) used for detection of replication-competent virus, including the detection limit and the acceptance criteria must be provided. Test and validation reports should be provided. When desired, the requirements with regard to test and validation reports can be discussed with the GMO office.

Section 2.13 (Provide a diagram ('map') of the clinical vector).

A map or description of the vector genome must be provided, with the emphasis on the modifications that have been made. The function and origin of the modified sequences must be described.

Section 2.14 (Molecular characterisation of the clinical vector). The aim of the molecular characterisation is to verify that the desired modification(s) is (are) present and that no undesirable modifications are present in the gmo (compared to the reference sequence) that might result in alterations in virulence, pathogenicity, tropism or transmission of the gmo.

The molecular characterisation should consist of a confirmation that the complete vector genome has been sequenced and the identity of the viral vector is confirmed. The applicant should describe whether deviations from the expected sequence are present, or not. If deviations are present, the applicant should state whether the observed deviations from the reference sequence are expected to influence the the environmental risk assessment. In case deviations are expected or known to have an impact on virulence, pathogenicity, tropism or transmission of the gmo, the environmental risks must be assessed. Note that it should be clear what is used as a reference sequence (e.g. an in silico prediction of the complete genome, or reference sequences as provided in the NCBI database).

The genetic stability of the virus must be addressed conform section 2.14 in the common application form.

Section 2.15 (Description of inserted sequences). Besides the information as requested in the common application form, also the origin of the sequences should be provided.

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. 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 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 in most cases 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 in most cases suffice.

Section 3.6a and 3.6b (Measures to prevent dissemination into the environment - Control measures during reconstitution (if applicable), handling and administration and Personal protective equipment). In cases where an apathogenic replication-deficient vector is used, a description that "*Standard hospital hygienic measures will be effective during reconstitution, handling and administration of the GMO and medical personnel will follow standard hospital hygienic measures."* will in most cases suffice. When a replication-competent or pathogenic vector is used the applicant should describe the required measures taking into account the characteristics of the GMO. For advice please contact the GMO office.

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 in most cases suffice.

Section 3.6d and 3.6e (Measures to prevent dissemination into the environment - Elimination or inactivation of left-overs of the finished product at the end of the clinical trial and Waste treatment). A description that "*All left-overs of the product will be disposed of as specific hospital waste or GMO-waste. All disposable waste that has been in contact with the GMO during preparation and administration will be disposed of as specific hospital waste or GMO-waste. Non-disposable materials are disinfected with appropriate validated disinfection detergents or autoclaved. Waste from sampling and sample processing is disposed of as specific hospital waste or GMO-waste."* will in most cases suffice. The applicant should determine the UN number that is applicable. For advice please contact the GMO office.

Section 3.7a (Sampling and further analyses of samples from study subjects - Describe how samples will be handled/stored/transported). Regarding storage and transport: a description that "*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 in most cases suffice. Regarding sampling: in cases where an apathogenic replication-deficient vector is used, a description that "*Standard hospital hygienic measures will be effective during sampling and handling/analysis of the samples"* will in most cases suffice. When a replication-competent or pathogenic vector is used the applicant should describe the required measures taking into account the characteristics of the GMO. For advice please contact the GMO office.

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 in most cases suffice. If samples are further analyzed under a contained use license, this can also be indicated.