Information required for an application according to § 74 of the Austrian Genetic Engineering Act (Gentechnikgesetz, GTG)

Information according to Annex I of the Austrian Directive on Deliberate Release 2005,BGBl. II Nr. 260/2005, in the version BGBl. II Nr. 193/2020, BGBLA_2020_II_193.pdf (verbrauchergesundheit.gv.at) for implementation of Directive 2001/18/EC

I. GENERAL INFORMATION

A. Name and address of the trial site / the applicant (name of clinic or institute)

B. Name, qualification and experience of the responsible principal investigator at this trial site, as well as general information on further personnel involved in the use of GMO for therapeutic purposes, including their qualification and experience.

C. Title of the project and short description / rationale of the clinical trial

II. INFORMATION RELATING TO THE GMO

A. Properties of the donor and recipient organisms (in most cases items 6-12 will only be relevant for the recipient organisms):

1. scientific name
2. taxonomic data
3. other names (trivial name, strain, etc.)
4. phenotypic and genetic markers/characteristics/features
5. information on the degree of relatedness (equivalent/related) between donor and recipient organisms
6. description of identification and detection techniques
7. information on the sensitivity, reliability (in quantitative terms) and specificity of detection and identification techniques
8. description of the natural habitat of the organism including information on host organisms and cellular tropism
9. organisms with which transfer of genetic material is known to occur under natural conditions
10. verification of the genetic stability of the organisms and factors affecting it
11. pathological and physiological traits:
    a. classification of hazard according to existing Community rules concerning the protection of human health and/or the environment (classification into a risk group)

b. -----

c. information on survivability in the environment

d. pathogenicity: infectivity, toxicity, virulence, allergenicity, ability of pathogen transfer, possible vectors, host range including non-target organisms. Possible activation of latent viruses (proviruses)

e. antibiotic resistances, potential use of these antibiotics in humans and pets for prophylaxis and therapy

f. involvement in environmental processes

12. Nature of naturally hosted indigenous vectors that are relevant to biological and environmental safety:

    a. -----

    b. Frequency of mobilisation (mobilisation frequency)

    c. specificity

    d. presence of genes which confer resistance

13. History of previous genetic modifications of the recipient organism

B. Characteristics of the vector

1. nature and source of the vector
2. genes/gene segments, vectors and non-coding nucleotide segments (vector backbone; expression cassette; regulatory elements such like promoters, enhancers, etc.; included gene sequences; transgenes; reporter genes; etc.) used to construct the GMO and to ensure the function of the introduced vector/insert in the GMO, including schematic representation of the vector construct (vector map)
3. possibility/frequency of mobilisation of the introduced vector; capability of gene transfer and methods used for its determination; possibility of recombination/reversion to replication-competent virus (especially replication competent lentivirus, RCL) or wild-type virus and detection methods
4. information on the degree to which the vector is limited to nucleotide sequences required to perform the intended function

C. Characteristics of the genetically modified organism

1. Information relating to the genetic modification:

    a. methods used for the genetic modification

    b. methods used to construct and introduce the novel insert(s) (transgenes, "genes of interest") into the recipient organism or to modify or delete nucleotide sequences in the recipient organism

c. Description of the inserted or modified nucleotide sequence(s); description of the construct and of the expression cassette

d. Information on the presence of any unknown sequences being included in the inserted nucleotide segments and information on the degree to which the inserted sequence is limited to the nucleotide sequence required to perform the intended function

e. selection criteria and selection methods

f. sequence, function and location of the altered, inserted, and/or deleted nucleotide sequence(s) in question, with particular reference to any known harmful sequences (pathogenic, oncogenic, toxic, allergenic, pharmacologically active)

2. Information on the final GMO used for therapeutic purposes:

   a. Description of the genetic traits or phenotypic characteristics caused by the genetic modification which may be expressed or no longer expressed

   b. structure and amount of any vector and/or donor DNA remaining in the final construction of the modified organism

   c. stability of the genetically modified traits of the GMO

   d. rate, level and possible tissue specificity of the expression of the genetically introduced genetic material or, if applicable, possible effects of genetically engineered deletions; indication of the measurement/detection methods and their degree of sensitivity

   e. activity and function of the expressed protein(s)

   f. methods for the identification and detection of the GMO, including methods for the identification and detection of the inserted or modified nucleotide sequences and of the vector

   g. specificity (for identification of the GMO and for distinction between donor and recipient organisms), sensitivity and reliability (quantitative information) of the detection and identification methods

   h. data or findings from clinical studies for therapeutic purposes using the same GMO or GMO combination, which have been previously approved or carried out or are currently being applied for or carried out within or outside Austria; citation of scientific publications on the results of clinical studies with relevant GMOs (e.g. comparable recipient organisms with the same genetically inserted material; same recipient organisms with comparable genetically inserted material)

   i. considerations in respect to human health and animal health, as well as plant health:

aa) pathogenic, toxic, allergenic or oncogenic effects of GMOs used for therapeutic purposes (even if they are no longer viable) and/or of their metabolic products,

bb) comparison of the GMO to the donor or recipient organisms with regard to pathogenicity

cc) capacity for colonisation

dd) if the GMO is pathogenic to humans being immunocompetent (having intact immune response):

- caused diseases and mechanism of pathogenicity, including invasiveness and virulence,

- transmissibility,

- infective dose,

- host range and possibility of its alteration,

- possibility of survival outside of the human host,

- presence of vectors or means of dissemination,

- biological stability,

- antibiotic resistance patterns,

- allergenicity,

- availability of appropriate therapies.

ee) other harmful properties of the gene products formed by the GMO due to the newly inserted nucleotide sequences

III. INFORMATION ON THE CONDITIONS FOR THE USE OF GMO FOR THERAPEUTIC PURPOSES AND ON THEREFORE RELEVANT PROPERTIES OF THE ENVIRONMENT

A. Information on the conditions for use of GMOs for therapeutic purposes

1. description of the intended use of GMOs for therapeutic purposes, including the objective(s) and the planned results
2. timeline for the use of GMO for therapeutic purposes, including expected timing(s), frequency and duration of GMO administration
3. safety precautions in the application area before and during GMO application
4. name of the premises where the application of the GMO(s) will take place (institute, clinic, university hospital, etc.) and description of the specific areas used for handling of the GMO(s) (storage, application and inactivation), i.e. building, floor, room number, intended use; site plan with identification of the rooms being used
5. method(s) to be used for the administration of the GMO(s)

6. quantity/concentration of the GMOs to be administered
7. -----
8. employee protection measures to protect personnel involved in the handling and administration of the GMO
9. treatment and disinfection measures of the application area after administration of the GMO
10. description of the measures foreseen for elimination or inactivation of the GMOs: Inactivation and elimination of GMOs after application; inactivation and elimination of solid and liquid GMO waste; decontamination, inactivation and/or elimination of utensils contaminated with GMOs, description of chemical or thermal inactivation methods used on site prior to off-site disposal
11. information on, and results of previous applications of the GMO(s) for therapeutic purposes, especially on applications at different scales (dose, time, pool of subjects, type of application) and for other purposes (other indication/disease).

B. Information on the properties of the environment relevant to the use of GMOs for therapeutic purposes (both in the area of application and if need be in any affected environment)

1. geographical location of the area of application and precise location information
2. -----
3. -----
4. -----
5. -----
6. -----
7. description of target and non-target organisms likely to be affected by an accidental release (e.g. shedding)
8. comparison of the natural habitat/host organism/tropism of the recipient organism with the target organism(s)/target organ(s)/target cell(s) intended in the context of the foreseen application
9. any known existing circumstances or facilities in the vicinity of the application area/site (e.g. livestock farms) that could affect the environmental impact of an accidental release

IV. INFORMATION RELATING TO THE INTERACTIONS BETWEEN THE GMOs AND THE ENVIRONMENT

A. Characteristics and conditions affecting survival, multiplication and dissemination

1. biological features of the GMO which affect survival, multiplication and dispersal
2. known or predicted environmental conditions which may affect survival, multiplication and dissemination of an unintentionally released GMO (surface conditions, temperature, humidity, pH, etc.)
3. sensitivity of the GMO to specific agents

B. Interactions with the environment

1. expected target area of the GMO
2. results from laboratory experiments on the possible behavior and properties of the GMO in the environment
3. genetic transfer capability of the GMO in the environment (humans, animals, environment) after unintentional release:
    a. Transfer of the genetically modified or inserted material from the GMO to other organisms
    b. Transfer of genetic material from naturally occurring organisms into the GMO
4. likelihood of selection of GMOs with undesirable traits after such gene transfer
5. measures employed to ensure and to verify genetic stability. Description of genetic traits that may prevent or minimize dispersal of genetically engineered material. Methods to verify genetic stability
6. known or expected modes of interaction with vectors; routes of biological dispersal, including inhalation, ingestion, contact, skin penetration, etc.
7. description of ecosystems in which the GMOs could reproduce
8. potential risk of excessive proliferation of GMOs in the environment
9. competitive and/or survival advantage of the GMOs in relation to the unmodified recipient organism(s)
10. identification and description of the target organisms (test subjects)
11. anticipated mechanisms and results of interaction between the released GMOs and the target organism(s) (test subjects)
12. identification and description of non-target organisms (e.g. medical personnel, persons living in the same household) which may be adversely affected by the unintended release (including shedding) of the GMO, and description of the

anticipated effects (risk of direct, indirect, immediate or delayed adverse effects on the health of third parties)

13. likelihood of shifts in biological interactions or host specificity in case of unintended release of the GMO
14. known or predicted interactions with non-target organisms in the environment (risk of direct, indirect, immediate or delayed adverse effects on the environment)
15. -----
16. other significant interactions with the environment

V. INFORMATION ON MONITORING, CONTROL, WASTE TREATMENT AND EMERGENCY RESPONSE PLANS

A. Monitoring techniques

1. Techniques, for detecting the GMO(s) and monitoring its/their effects
2. specificity (to identify the GMO(s) and distinguish them from the donor and recipient organisms), sensitivity and reliability of the monitoring techniques
3. techniques for detecting transfer of the introduced or modified genetic material to other organisms
4. duration and frequency of the monitoring of test subjects; timeframe for monitoring after the end of the trial

B. Control of the release

1. methods and procedures to avoid and/or minimize the spread of the GMO(s) beyond the intended experimental area, depending on the extent of the unintended release (especially shedding)
2. methods and procedures to protect the trial site from intrusion by unauthorized persons
3. methods and procedures to prevent other organisms from intrusion into the trial site of

C. Waste management

1. type of waste generated
2. expected amount of waste
3. description of the inactivation and disposal measures envisaged, according to the state of the art

D. Emergency response plans

1. methods and procedures for controlling the GMOs in case of unexpected spread beyond the experimental area
2. methods for the necessary decontamination of areas affected by the unexpected spread beyond the experimental area, e.g. decontamination procedures, measures for inactivation/disposal of the GMO(s)
3. methods for the treatment of humans, the environment, surfaces, etc. being exposed to the GMO during or after unexpected spread beyond the experimental area
4. methods for the isolation of the area affected by the unexpected spread beyond the experimental area
5. plans for protecting human health and the environment in case of the occurrence of undesirable effects.

SIMPLIFIED ENVIRONMENTAL RISK ASSESSMENT FOR THE USE OF GMO IN HUMAN FOR THERAPEUTIC PURPOSES

As far as the clinical investigational product for an intended therapeutic application for medical purposes in humans is a GMO product that

1. contains or consists of AAV vectors (vectors based on adeno-associated viruses), or

2. contains or consists of other viral vectors, or

3. contains or consists of human cells that have been genetically modified,

and for which a specific Environmental Risk Assessment is already available (see "GMO requirements for investigational products" at https://health.ec.europa.eu/medicinal-products/advanced-therapies_en), the information on the above questions (Information required for an application according to § 74 of the Austrian Genetic Engineering Act) can be replaced by the information in accordance with the respective specific Common Application Forms (CAF):

CAF for AAV vectors:
https://health.ec.europa.eu/system/files/2022-01/aavs_caf_en.pdf

CAF for viral vectors:
https://health.ec.europa.eu/system/files/2022-01/vvs_caf_en.pdf

CAF for genetically modified human cells:
https://health.ec.europa.eu/system/files/2021-11/gmcells_caf_en_0.pdf