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Guidance document Gene Therapy/GMO Environmental Data

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1 Terms, definitions, abbreviations

1.1 Definition of genetically modified microorganisms (GMOs)

In accordance with Article 22, paragraph 2 of ClinO, the definitions as stated in the Ordinance of 10 September 2008 (status on 1 January 2014) on the Handling of Organisms in the Environment (Release Ordinance, RO[1]) apply (Art. 3, let. a [Organisms], b [Microorganisms] d [genetically modified organisms]) and e [pathogenic organisms[).
Microorganisms are cellular or non-cellular microbiological entities able to replicate or transfer genetic material, in particular bacteria, algae, fungi, protozoa, viruses and viroids; legally equal are cell cultures, parasites, prions and biologically active genetic material, as well as mixtures and objects that contain such entities.
Pathogenic organisms are considered to be organisms that can cause diseases in human beings, livestock and useful plants, in wild flora or fauna or other organisms, as well as alien organisms that are also pathogenic.
Microorganisms are considered to be genetically modified if their genetic material has been altered by methods of gene technology in a way that does not occur under natural conditions by mating or natural recombination (for the definition of gene technology procedures, see the text of the Ordinance in Annex 2 of this document).
In this Guidance document, biologically active genetic material is considered to be DNA and RNA sequences that are not able to replicate independently (e.g. plasmids) but can be transferred and become infectious, or are constituted in such a way that they are capable of affecting an organism (e.g. targeted protein expression, provoking an immune response or affecting cell division).
In the context of clinical trials, genetically modified microorganisms or biologically active genetic material usually encompass:

- Viral vectors;
- Naked nucleic acids (e.g. plasmids);
- Complexed nucleic acids (e.g. plasmids complexed with the substance DEAE-Dextran);
- Bacterial vectors.

For the remainder, the above are referred to as investigational products.

2 Introduction

Guidance document for the compilation of the documentation on possible risks for humans and the environment in support of applications for the authorisation to carry out clinical trials of somatic gene therapy and with medicines containing genetically modified microorganisms (environmental data)

This Guidance document for Gene Therapy/GMO Environmental Data is intended to provide transparency for the applicant with respect to the documentation that must be provided along with the application for authorisation to the competent authority (Swissmedic) with the purpose of assessing the risk to humans and the environment from clinical trials of somatic gene therapy and of medicines containing genetically modified microorganisms.

[1] Release Ordinance, RO

The Guidance document takes into account the fact that the investigational products in question are usually viral vectors, plasmids or bacteria, and therefore focus on the risks of the investigational product being excreted by the trial subject and thus its potential release into the environment.
In this context, the Guidance document particularly stresses that the investigational product's replication capacity or reversion to replication capacity should be taken into account in the risk assessment.

The Guidance document makes a distinction between risk assessments for the following cases:
- In the „Documentation for the risk assessment for case A“, guidance is provided in the event that the investigational product is not excreted by trial participants;
- In part B, it is assumed that the investigational product will be excreted. The „Documentation for the risk assessment in case B1“ covers the situation where the investigational product is excreted but not released into the environment;
- „Documentation for the risk assessment for case B2“ covers the situation where the investigational product is released into the environment.

The Guidance document for Gene Therapy/GMO Environmental Data does not take into account requirements regarding the manufacturing process and the marketing authorisation for the investigational product. Furthermore, they do not address the risks for the trial participants.

2.1 Legal basis

This Guidance document for Gene Therapy/GMO Environmental Data is based on the Swiss Federal Act on Medicinal Products and Medical Devices of 15 December 2000 (Therapeutic Products Act, TPA [2]), the Federal Act on Research involving Human Beings (Human Research Act, HRA) of 30 September 2011 (Status as of 1 January 2014) [3] its implementing Ordinance on Clinical Trials in Human Research (Clinical Trials Ordinance; ClinO) of 20 September 2013 (Status as of 1 January 2014) [4] and the Federal Law of 21 March 2003 on Non-Human Gene Technology (Gene Technology Act, GTA [5]). Article 35, paragraph 7 of ClinO obliges Swissmedic, the Federal Office of Public Health (FOPH) and the Federal Office for the Environment (FOEN) to provide guidance on the assessment of risks for humans and the environment (see text of Art. 22 and 35 of ClinO in Annex 1 to this Guidance document).
The Guidance document applies to clinical trials during which genetic information is introduced into somatic cells (somatic gene therapy in accordance with Art. 22, para. 1 of ClinO), for clinical trials with medicinal products containing genetically modified microorganisms (Art. 22, para. 2 of ClinO) and for clinical trials with medicinal products containing pathogenic organisms as defined in the Release Ordinance (Art. 22, para. 3 of ClinO). For the remainder of the instructions, these types of trials will be referred to as „clinical trials“.
The Guidance document for Gene Therapy/GMO Environmental Data constitutes an Administrative Ordinance, which does not directly address the rights and obligations of individuals. Their objective is to permit the competent authority to carry out a risk assessment of clinical trials on an equal legal basis. By publishing the Guidance document, transparency is provided with respect to the environmental data that must be submitted to the competent authority in accordance with Article 35 of

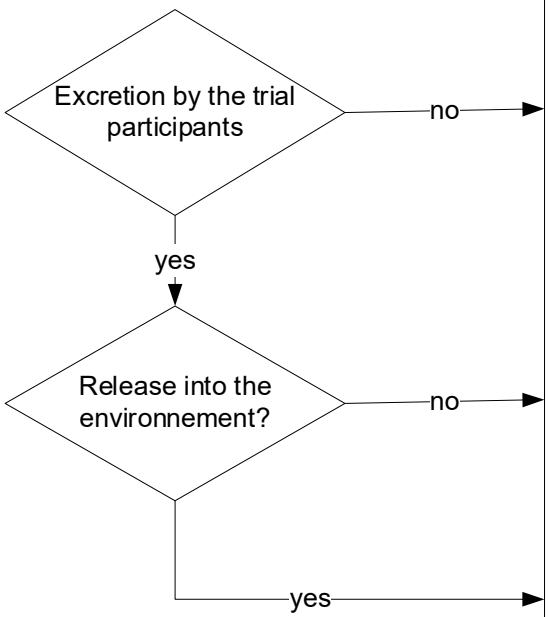
[2] Therapeutic Products Act, TPA (non-binding English translation)
[3] Human Research Act, HRA (non-binding English translation)
[4] Clinical Trials Ordinance, ClinO (non-binding English translation)
[5] Gene Technology Act, GTA (non-binding English translation)

ClinO. The instructions are intended to allow rapid and efficient evaluation of applications for clinical trials. For further documentation that must be submitted with the application for authorisation, see Annex 4, number 4 of ClinO and the Swissmedic Checklist I-315.AA.01-A12 Documents for TpP/GT/GMO clinical trials.
Annex 4, number 4 of ClinO states that a sponsor's application for authorisation must in particular include information necessary for the evaluation of the possible risks to humans and the environment (environmental data, see Annex 1 to this Guidance document). Environmental data encompasses all information that is required to demonstrate that humans and the environment are protected from hazards or impairment caused by clinical trials.
In accordance with Article 21, paragraph 1 of GTA, any handling of genetically modified organisms requires the authorisation of the relevant Federal authorities. The FOPH, FOEN and the SECB (must approve the clinical trial prior to an authorisation granted by Swissmedic. The authorisation requires an evaluation of the environmental data and the quality and biological safety of the product with regard to the participants and to human health and the environment (Art. 35, para. 4, let. a and b of ClinO). Swissmedic is the leading competent authority and carries out the procedures required for the authorisation.
The provisions of the Ordinance of 25 August 1999 (SAMV [6]) concerning the protection of workers against the risks connected to microorganisms apply to employees who come into contact with the investigational product.
It should be noted that the European Union has developed standards comparable to the GTA, the Ordinance of 25 August 1999 on the contained use of organisms (Containment Ordinance, ContainO [7]) and the SAMV (see EU Council Directive 98/81/EC [8] on the contained use of genetically modified microorganisms, European Parliament and Council Directive 2000/54/EC [9] on the protection of workers from risks related to exposure to biological agents at work, and also European Parliament and Council Directive 2001/18/EC [10] on the deliberate release into the environment of genetically modified organisms).
Information for the evaluation of the risks for the trial participants is not part of the environmental data and is therefore not covered by the present Guidance document (see Checklist I-315.AA.01-A12 Documents for TpP/GT/GMO clinical trials [11]).
Finally, the Guidance document does not cover the requirements relating to the manufacturing process or the marketing authorisation of the investigational product.

3 Other valid documents

Decision tree regarding the compilation of environmental data documentation

[6] SAMV (available in German, French and Italian)
[7] Containment Ordinance, ContainO (non-binding English translation)
[8] Council Directive 98/81/EC of 26 October 1998 amending Directive 90/219/EEC on the contained use of genetically modified micro-organisms
[9] Directive 2000/54/EC of the European Parliament and of the Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work (seventh individual directive within the meaning of Article 16(1) of Directive 89/391/EEC)
[10] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC - Commission Declaration
[11] https://www.swissmedic.ch/swissmedic/en/home/services/documents/transplant-products.html

Decision	Required documentation
Categorisation of the clinical trial depending on the behaviour of the investigational products following its administration to trial participants 	5.2.2 Documentation in accordance with case A 5.2.3 Documentation in accordance with case B1 5.2.4 Documentation in accordance with case B2 Description of the safety measures (in accordance with cases A, B1 or B2). In addition, the following must be submitted for each authorisation application: General information in accordance with 5.1 and the information with respect to storage, transport, preparation, administration, disposal of the investigational product

Selected international legal sources for additional information.

1. ACGM UK: Guidance from the Health and Safety Commission's Advisory Committee on Genetic Modification.
http://www.shef.ac.uk/safety/genereg/acgm.html

2. Commission de Génie Génétique, Commission d'étude de dissémination de produits issus de Génie Biomoléculaire, Agence Française de Sécurité Sanitaire des Produits de Santé :
Data Sheet for Clinical Trials Involving Gene Therapy Products (GTP) For Human Use.

3. EMA: Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products (Effective 13.01.2019).
https://www.ema.europa.eu/en/quality-preclinical-clinical-aspects-gene-therapy-medicinal-products

4. EMA Guideline: Guideline on Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal Products.
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003964.pdf

5. Euregenethy: Opinion paper on the current status of gene therapy regulation in Europe.
http://test.euregenethy.org/PDF/GT2002.pdf

6. ICH: ICH Considerations - General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors
http://www.ich.org/products/consideration-documents.html

7. NIH: NIH guideline for research involving recombinant or synthetic nucleic acid molecules
https://osp.od.nih.gov/biotechnology/biosafety-and-recombinant-dna-activities/

8. Recommendations of the SECB on the safe handling of human and animal cells and cell cultures
http://www.efbs.admin.ch/index.php?eID=tx_nawsecuredl&u=0&g=0&t=1398347957&hash=a650059516b7dd1649bfd59b86c397f031a18a57&file=fileadmin/_migrated/content_uploads/Zellkulturen_EFBS_E_01.pdf

4 Description - Environmental data documentation

4.1 General information

In order for an application to be approved, the general information in accordance with Annex 3 to this Guidance document must be submitted.

It is not necessary to repeat the general information in the environmental data documentation if it is already available elsewhere in the application and appropriate references are made.

The environmental data documentation must include the following aspects of handling of the investigational product:
- Storage;
- Transport;
- Preparation for administration to trial participants;
- Administration to trial participants;
- Monitoring the behaviour following administration to trial participants;
- Disposal.

For the above aspects, the safety measures in order to prevent the investigational product from being released into the environment and endangering humans and the environment must be documented.

4.2 Determining and evaluating the risks for humans and the environment (risk assessment)

4.2.1 Guidance for the risk assessment

For every aspect of handling, the risk assessment must include details of:
- The possible harmful effects of the investigational product (damage potential);
- The extent of the damage caused by the investigational product;
- The likelihood of damage and possible exposure of humans or the environment to the investigational product;
- The risks for humans or the environment (determined on the basis of the 3 points above);
- The required safety measures (measures to minimise the determined risk);
- The remaining risk when required safety measures are met.

The objective of a risk assessment is to determine and assess all possible direct, indirect, immediate or long-term harmful effects on humans and the environment if the investigational product is released.

The risk assessment must in particular include the investigational product's cumulative long-term effects and its replication capacity or reversion to replication capacity.

Extent and level of detail of the information for the risk assessment should be in accordance with the characteristics of the investigational product and depends primarily on whether the investigational product is excreted or not by the trial participants.

The risk assessment should be established on a case-by-case basis and on the basis of the latest scientific and technical methods and data.

The risk assessment must be repeated as soon as new information regarding the investigational product and its effects on humans or the environment is available.

Findings regarding the risks for humans and the environment from earlier clinical trials with the same investigational product should be listed and discussed.

More detailed explanations regarding risk assessment can be found in Annex 4 of this Guidance document.

As presented below, the documentation regarding the risk assessment must fulfil a number of requirements depending on whether or not the investigational product is excreted by the trial participants. If it is assumed that the investigational product will not be excreted by the trial participants, the risk assessment should be carried out in accordance with case A. If it is assumed that the investigational product will be excreted by the trial participants, the risk assessment should be carried out in accordance with cases B1 or B2 as appropriate.

4.2.1.1 Risk evaluation of gene therapy products that contain antibiotic-resistance genes

The use of antibiotic-resistance genes in gene therapy products is generally discouraged, especially if their use can jeopardize the success of clinical therapies in the target population. The infrequent use and the limited indication area cannot be equated with a minor clinical significance, because the significance of specific antibiotics can increase owing to the global rise in antibiotic-resistant bacteria.

If the antibiotic-resistance genes cannot be removed from the investigational products, the following conditions need to be met before an authorization can be granted:
- it must be justified why no alternative selection procedure suitable for the purpose but without antibiotic-resistance genes is used;
- the investigational product must not be excreted into the environment (case A or B1);
- the investigational product and the clinical trial must be of great significance.

In addition to detecting and assessing the risk for people and the environment, under sections 5.2.2 or 5.2.3, it must be evaluated whether there are significant risks in particular with regard to jeopardizing the use of those antibiotics in veterinary and human medicine. The instructions given in Annex 6 must be followed for this.

4.2.2 Documentation of the risk assessment for case A

Based on the assumption that no investigational products will be excreted by the trial participants

4.2.2.1 Information on biodistribution and excretion

The risk assessment for case A is based on:
- Information from previous clinical studies that confirm the assumption that the trial subject does not excrete the investigational product;
- Preclinical biodistribution studies using the investigational product (including data on excretion and on the potential for inadvertent germline integration);
- Biodistribution studies using comparable investigational products (including data on excretion and on the investigational product's potential for integrating the germline);

- Evaluation of the sensitivity of the analysis methods used in these studies;
- Any further justification for the assumption that the investigational product is not excreted, if biodistribution studies are not available, could be:
  - Favourable safety profile – for example rapid degradation – for specific investigational products;
  - Investigational product is replication deficient with low probability of reversion and does not recombine with wild type (in the trial subject);
  - Increased breakdown or lower tissue distribution pattern depending on type and site of administration;
  - Lower stability or increased degradation of the investigational product in the trial participants in general;
- Other relevant information.

4.2.2.2 Description of the risk to humans and the environment

If sufficient proof can be obtained that the investigational product is not excreted by the trial participants and there is no potential for integration in the germline, the risk of the clinical trial for humans and the environment can be considered negligible. If the excretion of the investigational product
cannot be reliably excluded, a risk assessment in accordance with B1 or B2 must be carried out.

4.2.2.3 Description of the safety measures required

The description of the safety measures should demonstrate that those measures prevent the release of GMO into the environment. This includes a description of the potential degradation products that are generated, the estimated quantity thereof, the planned disposal processes for the investigational product and the protective measures provided for persons who are dealing with the investigational product or are in contact with the trial participants (see Annex 4 no. 4.3 of ClinO).

4.2.3 Documentation of the risk assessment for case B1

Based on the assumption that investigational products will be excreted by the trial participants but shedding into the environment can be prevented.

4.2.3.1 Information regarding the safety conditions during the clinical trial for the trial participants

The risk assessment for case B1 is based on the results of preclinical and/or clinical biodistribution studies that indicate that the investigational product is excreted. The following points must be included:

- The nature and level of safety conditions which have to be applied for the accommodation of the trial participants during the clinical trial in order to prevent the release of the investigational product into the environment (e.g. accommodation, nature of the toilets/showers in the patients' rooms, etc.);
- Measures to avoid the release of the investigational product via persons coming into contact with the trial participants;
- Contact person's immune status to the investigational product (if necessary).

4.2.3.2 Description of the risk to humans and the environment

If valid data corroborate the assumption that the investigational product will be excreted by the trial participants within a limited period of time only (transient shedding), during which the trial participants are accommodated under conditions that prevent the investigational product from being released into the environment, it can be assumed that the risk of the clinical trial for humans and the environment is negligible for humans and the environment. The residual risk for the persons coming into contact with the investigational product must be defined.

4.2.3.3 Description of the safety measures required

The documentation consists of the description of:

- The safety measures to be deployed in order to prevent the release of excretion products into the environment;
- The methods used to monitor the trial participants in order to define the point as of which the excretion no longer takes place;
- The measures to be taken to protect the persons coming into contact with the investigational product and/or the trial participants.

4.2.4 Documentation of the risk assessment for case B2

Based on the assumption that investigational products will be excreted by the trial participants and shedding into the environment cannot be excluded.

4.2.4.1 Detailed information on the characteristics of the investigational product

The risk assessment for case B2 is based on preclinical and clinical studies on biodistribution and excretion. In addition, the following information should be submitted, if appropriate:

- Information in accordance with Annex 5 of this Guidance document. Particular emphasis should be placed on the forms of excretion, the quantity of active biological units excreted, the duration of the excretion and the persistence of excretion products in the environment (stability).

4.2.4.2 Description of the risk to humans and the environment

The risk assessment for case B2 is based on the assumption that the risk of the clinical trial to humans and the environment is not negligible if the investigational product is excreted by the trial participants over an extended period of time. This assumption is met if:

a) During the possible excretion period, the trial participants cannot be accommodated, under conditions that prevent the release of the investigational product into the environment and
b) The investigational product is sufficiently stable for its presence in the environment for a certain period of time, and in addition, e.g.:
   - Reveals an extended host range, a broader cell tropism or a modified transmission mode;
   - Has an increased infectivity or pathogenicity, for example due to a lesser susceptibility to be neutralised by the host's immune system;
   - Is replication competent or is likely to revert to a replication competent state;
   - Can recombine with wild types; or

- Has inserts that encode for a toxin, a cytokine, a growth factor or other factors that interfere with the cell cycle control (e.g. onco- and proto-oncogens[12]) and are regulated by a strong promoter/enhancer.

This requires a more detailed risk assessment in accordance with Annex 4 to this Guidance document.

4.2.4.3 Description of the safety measures required

If the investigational product is excreted into the environment by the trial participants, the documentation to be submitted, and in particular the safety measures to be taken, should include details of how the protection of humans and the environment can be guaranteed. The following points should be addressed:

- The methods for minimising or, if applicable, preventing the excretion;
- Measures to protect persons of coming into contact with the investigational product;
- Measures to protect humans and the environment in a broader sense (measures to control or correct unintentional dissemination);
- Methods to detect the investigational product in the environment and to monitor its effects;
- Specificity for identifying the investigational product, sensitivity, and reliability of the monitoring procedures.

5 Annex

5.1 Annex 1

Article 22 ClinO[13] Clinical trials of gene therapy and clinical trials of genetically modified or pathogenic organisms:

1 For the purposes of this Ordinance, clinical trials of gene therapy are trials in which genetic information is introduced into somatic cells (somatic gene therapy).

2 For the purposes of this Ordinance, clinical trials of genetically modified organisms are trials of medicinal products containing genetically modified organisms as defined in the Release Ordinance of 10 September 2008, and in particular replication-competent viruses.

3 For the purposes of this Ordinance, clinical trials of pathogenic organisms are trials of medicinal products containing pathogenic organisms as defined in the Release Ordinance.

4 For clinical trials of gene therapy and for clinical trials of genetically modified or pathogenic organisms, the provisions of this Ordinance concerning clinical trials of medicinal products apply mutatis mutandis

Article 35 ClinO Clinical trials of gene therapy and clinical trials of genetically modified or pathogenic organisms:

[12] A possible reference for assisting with the risk assessment is also that of the statement by the Swiss Expert Commission for Biosafety (http://www.efbs.ch) on risk assessment of activities with oncogenic and cytokine encoding sequences (http://www.efbs.admin.ch/en/documentation/statements-on-permit-applications)

[13] Clinical Trials Ordinance, ClinO (non-binding English translation)

1. For Category B and C clinical trials of gene therapy and for clinical trials of genetically modified or pathogenic organisms as defined in Article 22, the documents specified in Annex 4 number 4 must be submitted to Swissmedic.
2. Before granting authorisation, Swissmedic shall seek opinions from the Swiss Expert Committee for Biosafety (SECB), the Federal Office for the Environment (FOEN) and the FOPH.
3. In addition to the areas specified in Article 32, it shall review whether the quality and biological safety of the product are guaranteed with regard to the participants and to human health and the environment.
4. It shall grant authorisation if:
   a. the SECB has confirmed the quality and biological safety of the product with regard to the participants and to human health and the environment; and
   b. no objections to the clinical trial have been raised by the FOPH or by the FOEN, based on the assessment of the environmental data.
5. Swissmedic shall grant authorisation within 60 days of acknowledgement of receipt of the formally correct application documents. Swissmedic shall inform the competent federal and cantonal authorities of its decision.
6. Authorisations shall remain valid for the duration of the clinical trial, but for no longer than five years after they are granted.
7 Swissmedic, the FOPH and the FOEN shall jointly issue guidelines on assessment of risks to human health and the environment.

Annex 4 number 4 ClinO Additional application documents for Category B and C clinical trials of gene therapy and of genetically modified or pathogenic organisms:

4.1 Information on the risks of the investigational product containing genetically modified or pathogenic organisms;
4.2 risk assessment of the conduct of the clinical trial with regard to the protection of human health and the environment;
4.3 a description of the safety measures required for the protection of human and animal health and the environment, and in particular to prevent the release of microorganisms into the environment during and after transplantation, and during transport, storage and disposal.

5.2 Annex 2

Definition of gene technology methods (according to Annex 1, RO/FrSV [14]), (ContainO/ESV [15]) and (SAMV [16]):

1 Gene technology methods means, in particular:
   a. recombinant nucleic acid techniques, in which nucleic acid molecules synthesised outside the organism are inserted into viruses, bacterial plasmids or other vector systems to produce novel combinations of genetic material, which are then transferred to a recipient (host) organism in which they would not naturally occur but are capable of continued propagation;

[14] Release Ordinance, RO (non-binding English translation)
[15] Containment Ordinance, ContainO (non-binding English translation)
[16] SAMV (available in German, French and Italian)

b. techniques in which genetic material produced outside the organism is inserted directly into an organism, in particular by microinjection, macroinjection and microencapsulation, electroporation or on microprojectiles;
c. cell fusion or hybridisation techniques in which cells with novel combinations of genetic material are produced by the fusion of two or more cells through processes that do not occur under natural conditions.

2 Self-cloning of pathogenic organisms shall be regarded as a method of gene technology. This consists of the removal of nucleic acid sequences from one cell of an organism and the complete or partial insertion of this nucleic acid or a synthetic equivalent (possibly after a previous enzymatic or mechanical treatment) into cells of the same species or cells which are closely related phylogenetically and which can exchange genetic material by natural physiological processes.

3 Self-cloning of non-pathogenic organisms and the following methods shall not be regarded as methods of gene technology, as long as they are not used in association with recombinant nucleic acid molecules or genetically modified organisms:
a. mutagenesis;
b. cell and protoplast fusion of prokaryotic microorganisms that exchange genetic material by natural physiological processes;
c. cell and protoplast fusion of eukaryotic cells, including the production of hybridoma cell lines and the fusion of plant cells;
d. in vitro fertilisation;
e. natural processes such as conjugation, transduction and transformation;
f. changes in ploidy level, including aneuploidy and the elimination of chromosomes.

5.3 nnex 3

General information:

It is not mandatory to provide the general information of the environmental data if this is already available elsewhere within the application and appropriate reference are made. The general information includes:

- Name and address of the applicant;
- Name, address and qualification of those carrying out the clinical trials;
- Title and description of the project, including the objectives;
- Number of trial participants and duration of the clinical trial;
- Name of the investigational product;
- Detailed description of the characteristics of the investigational product and how it is manufactured.

The information relating to the characteristics of the investigational product should, in particular, cover the following points:

1. Donor and recipient organism
   - Scientific description and taxonomic data;
   - Characteristics of the micro-organism:
     - Pathogenicity and other adverse effects;

  - Description of the phenotype and any genetic modifications compared with the starting material (in particular resistance to antibiotics);
  - Genetic stability;
- Detection and identification procedures.

2. Vector systems
   - Vectors used to manufacture the investigational product;
   - Type and origin of the vectors;
   - Characteristics of the vector sequence combination;
   - Transfer methods used.

3. Insert or nucleic acid sequence used
   - Encoding sequence(s), geno- and phenotype markers;
   - Level of expression of the sequence introduced, characteristics and activity of the protein brought to expression (harmful effects);
   - Localisation of the sequence that is introduced or changed;
   - Purity of the insert in relation to unknown sequences and pertinent information regarding the extent to which the sequence introduced is restricted to the DNA that is required to fulfil the planned function.

4. Description of the investigational product, in particular the genetic features, their stability and the new phenotypical characteristics (reversion to replication capacity, recombination with wild type, complementation) as well as a description of the identification and detection procedures.

5. Findings regarding the risks for humans and the environment from earlier clinical trials with the same or comparable investigational products should also be included in the general information.

5.4 Annex 4

Basic principles for carrying out the risk assessment relating to clinical trials of somatic gene therapy and medicines containing genetically modified microorganisms:

The information below has been compiled based on the Ordinance of 10. September 2008 (status 1 January 2014) on the release of organisms into the environment (Release Ordinance, RO [17]). EU Directive 2001/18/EC and EU Guideline „Environmental Risk Assessment for Human Medicinal Products Containing or Consisting of GMOs“ (Reference in Annex 7) were also taken into consideration.

1 Determination of the potential adverse effects of the investigational product (damage potential)

All properties of the investigational product that are related to genetic modification and that are potentially harmful to humans or to the environment must be determined (see also Annexes 3 and 5). In doing so, no potentially harmful effects on humans and the environment should be omitted because they are considered unlikely to occur.
Information on earlier clinical trials with similar genetically modified microorganisms or similar biologically active genetic materials and their interaction under similar conditions in humans and the environment should also be taken into account in the risk assessment.

[17] Release Ordinance, RO (non-binding English translation)

Possible direct or indirect (e.g. as a result of the investigational product being disseminated in the environment) harmful effects are, for example:

- Illness in humans, animals and plants, including allergenic and toxic effects (including activation of cellular proto-oncogenes by the insertion of a vector into the genome);
- Changed sensitivity to pathogens whereby the propagation of contagious illnesses and / or the creation of new reservoirs or vectors is facilitated (e.g. because of changes to the host spectrum, the tissue specificity or interaction with the immune system);
- Endangering prophylaxis or therapy in the fields of human and animal medicine and of plant protection (e.g. development of resistance to antibiotics);
- Regained virulence as a result of genetic instability (e.g. reversion to replication capacity or competency to recombine with wild type);
- Dissemination and reproduction of the investigational product within the environment;
- Possible gene transfer to non-target organisms.

2 Determination of the extent of possible damage from the investigational product

In addition to determining the damage potential, the extent of the possible harmful effects on humans and the environment should be evaluated. Particular consideration should be given to:

- Whether individuals, large sections of the population, or the environment are affected;
- Whether the effect is limited in time or long-term;
- Whether the damage is reversible or irreversible.

The assessment of the damage should be quantified as negligible, low, medium, or severe.

3 Determining the probability of damage occurring and of possible exposure to the investigational product

The probability of the various possible harmful effects occurring should be determined and, where possible, evaluated (negligible, low, medium, high).

The type of possible release (e.g. from the administration or excretion of the investigational product) and the characteristics of the environment in which the investigational product could be released play an important role in the evaluation of the possible damage and the probability of it occurring. The probability of its occurrence is also influenced by the behaviour of the persons coming into contact with the investigational product or any products excreted by the trial participants. Possible effects on immune-compromised or particularly sensitive individuals must be taken into account.

4 Estimation of the risk for humans and the environment in the case of a possible release of the investigational product

The term „risk“ should be used in relation to the probability of such occurrences involving the product and the extent of the damage caused. The possible immediate or longer-term effects on humans and the environment as a result of direct or indirect interaction with the investigational product must be determined. Attention must be paid in particular to those persons taking part in the clinical trial, those who could come into contact with the investigational product and the environment that could be affected by an excretion. The various individual risks should be determined initially, followed by the overall risk. The following table may be used to assist in determining the risk.

		Probability			
		High	**Medium**	**Low**	**Negligible**
Extent	**Severe**	High	High	Medium	None
	Medium	High	Medium	Medium/Low	None
	Low	Medium/Low	Low	Low	None
	Negligible	None	None	None	None

5 Determining the safety measures required (measures to minimise the risks determined)

The safety measures needed to protect humans and the environment must be determined on the basis of the damage potential, the extent of possible damage, the probability of occurrence and the resulting risks.

In particular, the measures to limit the duration and area affected by any release into the environment should be determined (monitoring and control measures, waste disposal and emergency plans).

6 Overall risk assessment for humans and the environment

An overall risk assessment for humans and the environment, taking into account the extent and probability of the potential damage and the safety measures to be implemented, must be established.

5.5 Annex 5

Information on risk assessment for humans and the environment in the case the investigational product is excreted and there is an increased risk of it escaping into the environment:

In line with Annex III A of European Parliament and Council Directive 2001/18/EC[18] and with the „Data Sheet for Clinical Trials Involving Gene Therapy Products (GTP) For Human Use“ issued by the Agence Française de Sécurité Sanitaire des Produits de Santé (Reference in Annex 7), the following information should be submitted.

I Characteristics of the investigational product in regard to possible effects on humans and the environment

1. Pathogenicity for humans, animals or plants:
   - Illnesses caused;
   - Mechanism of pathogenicity;
   - Invasiveness, virulence, infectiousness, infective dose;
   - Availability of appropriate therapies;
   - Resistance/sensitivity to antibiotic reagents;
   - Effects of metabolic products;
   - Toxic or allergenic effects.
2. Host range, tropism, capacity for colonisation;
3. Possibility of survival outside of human host;
4. Possible interaction with non-host organisms (animals and plants);
5. Emission of virulence genes;

[18] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC - Commission Declaration

6. Comparison / relationship with microorganisms occurring naturally;
7. Competitive advantage in relation to microorganisms occurring naturally;
8. Genetic stability, e.g.:
   - Possibility of genetic modification in the environment;
   - Absorption and integration of genetic material (incl. recombination competency with wild type);
   - Replication capacity, likelihood of reversion to replication capacity.
9. Other relevant characteristics.

II Interactions between the investigational product and humans

1. Means of release, known or possible forms of interaction with the investigational product including inhalation, ingestion, surface contact, sexual transmission, intravenous injection, administration of blood products;
2. Immune status of persons coming into contact with the investigational product (notably medical staff);
3. Behaviour of the investigational product in trial participants or in persons coming into close contact with trial participants (urine, faeces, nasal secretion, semen, sputum, blood);
4. Possible persistence of the investigational product under specific conditions in trial participants or in persons coming into close contact with trial participants.

III Interactions between the investigational product and the environment

1. Potential for amplification or release into the environment;
2. Capacity for gene transfer by absorption of the genetic material by microorganisms or recombination with other microorganisms, trans-complementation, reactivation, interference;

3. Expected mechanism and result of the interaction with host organisms and the ecological effects, in particular:
   - Capacity for gene transfer;
   - Likelihood of a selection;
4. Description of the genetic features that prevent the dissemination of genetic material or that restrict it to a minimum;
5. Description of the ecosystems concerned;
6. Likelihood of modifications to the biological interactions or in the host organisms' range when released;
7. Known or predicted involvement in bio-geochemical processes.

5.6 Annex 6

Risk assessment for gene therapy products that contain antibiotic resistance genes:

In addition to the information mentioned under sections 5.2.2, 5.2.3 and 5.2.4, the following information is necessary to assess the risks of gene therapy products that contain antibiotic resistance genes:

Information on the properties of the gene sequences

- Functionality: does the gene sequence correspond to a functional antibiotic resistance product?
- Possibility for homologous recombination: can horizontal gene transfer be expected?
- Preceded by prokaryotic/eukaryotic promoters: what is the probability that the gene sequence could be expressed in microorganisms and the cells of the trial subject?
- Stability: is the gene sequence broken down into non-functional units? How fast and how complete is the break-down?

Information on the medical use of these antibiotics

- Are these antibiotics used in human/veterinary medicine?
- Are the antibiotics effective against a broad spectrum of microorganisms, or a specific strain of microorganism?
- Are resistance developments known?
- If resistance develops, are replacement antibiotics available in the same or other substance classes?
- If resistance develops, is the efficacy of other antibiotics compromised (through cross-resistance)?
- Are the antibiotics considered as last-resort antibiotics for certain infectious diseases (multiple-drug resistant microorganisms) or is it presumed that they can be considered as such with the progressive development of multiple-drug resistance?

Information about excretion

- Can it be shown by means of experimental trials or pre-clinical studies that, after use by the trial participants as part of the clinical trial or after licensing, the investigational product is not excreted and released into the environment, or can excretion and release into the environment be prevented by taking appropriate measures in the treatment of the trial participants or, after licensing, the patients?

Information about presence in the environment

- Are the antibiotic resistance genes naturally present in the environment or common in the environment?

The information and conclusions mentioned in this section regarding risks and security measures should, depending on the type of gene therapy (A, B1), be integrated in the evaluation under sections 5.2.2 and 5.2.3.

Change history

Version	Change	sig
5.0	Transfer ATM processes in the area of authorisations New ID number assigned Formal adjustments, new layout	dei