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| --- | --- | --- |
| **Application form for clinical research with human cells genetically modified by means of lentiviral vectors conform article 39c of the Regeling ggo[[1]](#footnote-1)**   * This application form can only be used for human cells genetically modified by means of lentiviral vectors in cases where the proposed work is conform article 39c of the Regeling ggo. It follows that:  1. there is no risk of formation of replication competent virus; 2. residual infectious viral vector particles that are capable of being released in the environment may be present; 3. the applied vector is a SIN, third generation lentiviral vector derived from HIV-1, pseudotyped with VSV-G.  * This application form serves to provide the necessary information in accordance with article 40c of the Regeling ggo. In this application form, a number of questions that follow from the *Common application form for clinical research with human cells genetically modified by means of viral vectors, Version 4, December 2020* do not apply. These fields are indicated with a N/A (not applicable). A number of questions are already answered in accordance with Bijlage 10, Deel D Artikel D:5 – D:8 of the Regeling ggo. * In accordance with the GDPR ((EU) 2016/679), a separate general personal data form (*Algemene persoonsgegevens*) is used for personal information (see website Loket Gentherapie). * The granting of a GMO-permit is a public procedure and therefore all information provided in the application is public. Information about keeping data confidential and how this must be requested can be found on the website (see website Loket Gentherapie). * For a clarification of the necessary substantive information, a “tips & tricks” is available on the website Loket Gentherapie. * The application form must be accompanied by a Part B Summary Notification Information Format (SNIF B) (online via E-submission Food Chain platform) * Contact:   + Internet: [www.ggo-vergunningverlening.nl](http://www.ggo-vergunningverlening.nl) / www.loketgentherapie.nl   + Email: [bggo@rivm.nl](mailto:bggo@rivm.nl)   + Telephone: 0031 (0)88-689 7099 | | |
| **Document**  **history** | **Publication**  **Date** | **Description of main changes** |
| Version 1.0[[2]](#footnote-2) | October 2021 |  |
| Version 1.1 | December 2022 | change in SNIF submission procedure |
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**APPLICATION FORM FOR CLINICAL RESEARCH WITH HUMAN CELLS GENETICALLY MODIFIED BY MEANS OF RETRO/LENTIVIRAL VECTORS CONFORM ARTICLE 39c OF THE REGELING GGO MILIEUBEHEER 2013**

# SECTION 1 ADMINISTRATIVE INFORMATION

**1.1 Identification of the applicant:**

|  |  |
| --- | --- |
| **Organisation Name:** | *Fill in the name of the legal entity* |
| **Address Details:** | *Fill in the address of the legal entity* |
| **Contact person:** | N/A |
| **Telephone No:** | N/A |
| **Email Address:** | N/A |

* 1. **Identification of the sponsor (to the extent that is different from the applicant):**

|  |  |
| --- | --- |
| **Organisation Name:** | N/A |
| **Address Details:** | N/A |
| **Contact person:** | N/A |
| **Telephone No:** | N/A |
| **Email Address:** | N/A |

* 1. **Information about the clinical trial:**

1. **General information about the clinical trial:**

|  |  |
| --- | --- |
| **EudraCT-number (where available):** | N/A |
| **Deliberate release reference number (where available and applicable):** |  |
| **Title of the clinical trial:** | *Provide a title that covers the proposed work.* |
| **Name of principal investigator:** | ***This information may be provided in the annex with confidential information.*** |
| **Objective of the study:** | *Provide the objective(s) of the proposed work.* |
| **Intended start and end date:** | N/A |
| **Number of trial subjects that will take part in the study:** | N/A |
| **Indicate if an application related to the same investigational medicinal product has been submitted -or is planned to be submitted- to other EEA Member States. In the affirmative, please identify the countries concerned:** | N/A |

# Intended location(s) of the study:

The applicant should provide information about the sites located in the country of submission of the application. In addition to the location of the clinical activities, the location(s) of laboratories in which activities with the GMO are carried out under the terms of this application should be stated (e.g. location of storage of the investigational medicinal product, location of storage of samples from clinical trial subjects that contain GMOs).

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| --- | --- |
| **Organisation Name:** | *Fill in the place(s) where the work will be performed. This is the location(s) (i.e. location name and visiting address) where the work, under responsibility of the applicant, will be performed.* |
| **Address Details:** |  |
| **Contact person:** | N/A |
| **Telephone No:** | N/A |
| **Email Address:** | N/A |
| **Planned activities:** | N/A |
| **Containment level:** | N/A |
| **Name and contact details of the responsible person:** | N/A |

# Logistics for transportation:

The applicant should provide information about the logistics for in-house transportation.

|  |
| --- |
| *In-house transport of the medical product takes place in a closed, break-proof, leak-proof packaging.*  *In-house transport of samples taken from the test subjects that may contain the medical product takes place conform the transport of regular patient samples.* |

# SECTION 2 INFORMATION ABOUT THE INVESTIGATIONAL MEDICINAL PRODUCT

* 1. **Characterisation of the finished investigational medicinal product.**

1. **General information:**

|  |  |
| --- | --- |
| **Description of the finished medicinal product** | Autologous □  Allogeneic □ |
| Specify type of cells (*e.g*. hematopoietic stem cells…):  ………………………………………………………………………. |
| **Viral vector used**: Retrovirus   Lentivirus[[3]](#footnote-3) x |
| **Pharmaceutical**  **form:** | N/A |
| **Mode of**  **administration:** | *Fill in the mode of administration.* |

1. **Absence of replication competent virus particles in the finished product:**

The applicant should demonstrate absence of formation of replication competent virus at the level of the viral production system or, alternatively, demonstration of absence of replication competent virus in the transduced cells in accordance with the Good Practice on the assessment of GMO-related aspects in the context of clinical trials with human cells genetically modified by means of retro/lentiviral vectors.

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| Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.  *N/A.  A third generation SIN lentiviral vector production system is used for production of the genetically modified cells. Using this production system formation of RCL is not possible. Conform COGEM advice CGM/190729-01 RCL testing will be waived as the chance of formation of RCL is negligible and no RCL will be present in the finished product.* |

1. **Presence of residual infectious viral vector particles in the finished product:**

The applicant should demonstrate that a maximum of 1\*1012 lentiviral particles are present in the medical product, in accordance with article D:5, section 5 of the Regeling ggo.

Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.

Provide information about the amount of lentiviral particles present in the medical product to be administered to the subject (max 1\*1012).

# 2.2 Molecular characterisation of the applied vectors.

1. **Map of the construct:**

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| --- |
| Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.  Describe the viral vector genome and the molecular characterization of the vector. |

1. **Description of each of the components of the vector:**

The applicant should provide a detailed description of each of the components of the vector used.

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| Confidential information should be provided in an annex, together with the reasons why it is considered confidential. The Section of the application form to which the information refers should be clearly identified. When confidentially is claimed, a summary that can be made public should be provided in this section.  From article 39c of the Regeling ggo it follows that:   * The producer cells used are free of HIV-1, HIV-2, HTLV-1, HTLV-2, and other relevant lentiviruses that can lead to complementation or recombination of the lentiviral vector. * *The genetically modified lentiviral particles and the genetically modified human cells are produced under (current) Good Manufacturing Practice (GMP) or under the principles of (current) GMP.* * *The transgene used does not encode sequences capable of complementing the replication deficient lentiviral vector. The transgene used is free from harmful sequences.* * *The applied vector is a third generation lentiviral vector based on HIV-1. The LTRs in the viral genome are self-inactivating (SIN).*   Describe the production system of the lentiviral vector. |

# SECTION 3- CONTROL MEASURES

* 1. **Measures to prevent risks of accidental transfer during administration to health care professionals and other staff involved in the transport/handling/administration of the product:**

The applicant should provide an overview of relevant (hospital hygiene) measures that will be taken, including personal protective equipment and a description of measures to take in case of accidental self-administration of the investigational medicinal product (e.g. needle stick).

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| *The medical product is stored in a closed, break-proof, leak-proof double container in a room with limited access.*  *Preparation and administration of the medical product takes place conform standard hospital hygiene measures.*  *Medical personnel will follow standard hospital hygienic measures.*  *Standard hospital hygienic measures will be effective during sampling and further analyses.*  *Samples from the test subjects that may contain the medical product will be stored conform the storage of regular patient samples.* |

# Risk minimisation strategies regarding patients:

The applicant should explain if it is considered that patients should be prevented from donating blood/cells/tissues/organs after being administered the genetically modified human cells.

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| --- |
| N/A |

# Measures to prevent dissemination into the environment:

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| --- | --- |
| **Decontamination/cleaning measures after administration:** | *Non-disposable materials are disinfected with appropriate validated disinfection detergents or autoclaved. In case of spilling, contaminated surfaces are disinfected with a suitable validated disinfectant.* |
| **Elimination or inactivation of left-overs of the finished product at the end of the clinical trial:** | *Waste that contains the medical product or has been in contact with the medical product during preparation and administration is disposed of as specific hospital waste or as waste containing GMO’s.* |
| **Waste treatment:** | *All disposable waste that has been in contact with the medical product during preparation and administration will be disposed of as specific hospital waste or as waste containing GMO’s.*  *Waste from samples, from sampling and from processing of samples from the subjects that may contain the medical product, is disposed of as specific hospital waste or as waste containing GMOs.* |

* 1. **Other risk minimisation measures:**

This section should only be completed if the applicant considers that there are additional risk minimisation measures that should be implemented.

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| --- | --- |
| **Identified risk(s)** | **Risk minimisation measure(s)** |
|  | In accordance with Bijlage 10, Deel D, of the Regeling ggo, the following risk minimization measures will be applied:   * *Following administration of the medicinal product the test subject should remain in the hospital for at least 16 hours to ensure that the standard hospital hygiene measures are taken;* * *After administration of the medicinal product the infusion site will be disinfected adequately to inactivate any residing vector particles, and standard hospital hygiene measures during the care of the test subject are taken;* * *The test subject, medical personnel and visitors should be informed about protocols and safety measures during the first 16 hours after administration of the medicinal product.* |

# SECTION 4- ENVIRONMENTAL RISK ASSESSMENT

**Specific environmental risk assessment:**

Considering the specific characteristics of the investigational medicinal product (as described in Section 2), the applicant considers that investigational medicinal product falls under the provisions of article 39c of the Regeling ggo, and that the standardized environmental risk assessment as described in Bijlage 1 to the explanation of the regulation to amend the Regeling ggo[[4]](#footnote-4) and the associated conditions described in Bijlage 10, Deel D (article D:1 – D:10) apply:

Yes □

No □

If the answer to the above is “No”, the work cannot be applied for under article 3.26a of the Besluit ggo[[5]](#footnote-5) and the applicant should apply for a GMO-permit conform the regular procedure for GMOs under article 3.10 of the Besluit ggo.

1. Regeling genetisch gemodificeerde organismen milieubeheer 2013 (Regeling ggo) [↑](#footnote-ref-1)
2. This form follows the structure of the relevant questions as established in the *Common application form for clinical research with human cells genetically modified by means of viral vectors, Version 4, December 2020*. This form applies to applications that are in accordance with article 3.26a of the Besluit ggo and ggo and they are dealt with in accordance with article 3.24 of the Besluit ggo. [↑](#footnote-ref-2)
3. Viral vectors derived from human immunodeficiency virus-1 (HIV-1) conform COGEM advice CGM/201214-02. [↑](#footnote-ref-3)
4. [Staatscourant 2021 nr. 40449 16 september 2021](https://zoek.officielebekendmakingen.nl/stcrt-2021-40449.pdf) [↑](#footnote-ref-4)
5. Besluit genetisch gemodificeerde organismen milieubeheer 2013 [↑](#footnote-ref-5)