Environmental Protection Authority
Te Mana Rauhī Taiao

New Zealand Government

Decision

Date	21 August 2020
Application number	APP204075
Application type	To develop in containment genetically modified organisms under sections 40(1) and 42A of the Hazardous Substances and New Organisms Act 1996
Applicant	The Malaghan Institute of Medical Research
Date Application received	7 August 2020
Consideration date	20 August 2020
Considered by	Siobhan Quayle, Group General Manager, Regulatory Systems and Operations[1]
Purpose of the Application	To develop genetically modified human cells for the packaging and testing of 3rd generation self-inactivating lentiviral vectors, to be used to genetically modify human T cells for the expression of genes that regulate the activity of human immune cells.

1. Summary of Decision

1.1. Application APP204075 to develop, as a project, genetically modified organisms (as described in Table 1 and Schedule of this decision) in containment is **approved, with controls**.

1.2. I had sufficient information to assess the application. The application was considered in accordance with section 42A of the Hazardous Substances and New Organisms (HSNO) Act

[1] The Group General Manager of Regulatory Systems and Operations has made the decision on this application under delegated authority in accordance with section 19 of the Act.

1996 (“the Act”), the Hazardous Substances and New Organisms (Low-Risk Genetic Modification) Regulations 2003 (“the Regulations”), and the Hazardous Substances and New Organisms (Methodology) Order 1998 (“the Methodology”).

1.3. The application was formally received on 7 August 2020.

2. The approved genetically modified organisms (GMOs) and the controls imposed

Purpose of the project

2.1. The purpose of this application is to develop genetically modified cultured human cell lines using 3rd generation self-inactivating lentiviral vectors. The application seeks to enable the genetic modification of human lentiviral packaging cell lines, leukaemia cell lines for vector titre testing, and human primary T cells with genes encoding Chimaeric Antigen Receptors, which recognise and bind the cell surface protein CD19, and activate the receptor co-stimulatory domains, thus killing B-cell leukaemia cancer cells.

2.2. I determined that this application is for a valid purpose: the development of any new organism as provided for in section 39(1)(a) of the Act.

Description of the organisms to be developed

2.3. As per section 42A(2) of the Act, I was satisfied that the host organisms and the proposed genetic modifications conform to the requirements of:

- Category 1 host organisms (as per clause 7 of the Regulations), and
- Category B genetic modifications (as per clause 5 of the Regulations) (as described in Table 1).

Table 1: Approved organism description

Host organisms	Cultured cell lines of the following species: *Homo sapiens* L. 1758 (human). Human lentiviral packaging cell lines, primary leukaemia cell lines for vector titre testing, and human primary T cells with genes encoding Chimaeric Antigen Receptors
Category of host organism	These organisms are Category 1 host organisms because: • they are clearly identifiable and classifiable • they are characterised to the extent that their main biological characteristics are known • they are not normally able to (and do not contain infectious agents normally able to) cause disease in humans, animals, plants or fungi • they do not normally infect, colonise or establish in humans, and • they do not produce desiccation-resistant structures such as spores or cysts that can be normally disseminated in the air.

Modification	Vectors will be 3rd generation replication-defective self-inactivating lentiviral vectors and consist of plasmids containing viral packaging gene constructs, envelope protein constructs, and transfer vectors containing: promoters and gene regulatory elements, packaging signals, secretory signals, polyadenylation signals, flanking long terminal repeat sequences and origins of replication, genes for viral envelope proteins, reverse transcriptase, integrase, matrix, capsid and nucleocapsid proteins, envelope proteins, protease. Donor genetic material is sourced from humans, and mammalian viruses. The modifications will consist of functional coding sequences for chimaeric antigen receptors, including antibody single chain variable fragment recognising the CD19 cell surface protein, transmembrane domains, and immune cell co-stimulatory domains. The modifications will exclude: • Genetic material that increases the pathogenicity, virulence, or infectivity of the host organism • Genes that encode for vertebrate toxins with an LD_{50} < 100 µg/kg, and • Those that result in the GMO having a greater ability to escape from containment than the unmodified host organism.
Category of modification	The modifications are Category B because these modifications are carried out under a minimum of PC2 containment as defined in the Regulations. They do not increase the pathogenicity, virulence or infectivity of the host organism to laboratory personnel, the community or the environment and do not result in the GMO having a greater ability to escape from containment than the unmodified host organism.
Minimum containment level required	PC2

2.4. I considered that this project represents a particular line of scientific inquiry and has clearly defined objectives to develop human lentiviral vector packaging cell lines from humans, with transgenes encoding Chimaeric Antigen Receptors, specified in Table 1, within a containment structure. This will allow the research described above. I determined that the organism description in this application falls within the bounds of a project for the development of GMOs. This is because it complies with the requirements of the Regulations as described above.

3. Rapid assessment of the adverse effects of the project

3.1. As I am satisfied that the host organisms and genetic modifications meet the criteria of low risk genetic modification (as per the Regulations) and, per section 42A(2) of the Act, I have made a rapid assessment of the adverse effects of carrying out the project as follows.

3.2. I note that the GMOs would first need to escape from the containment facility into the environment to cause non-negligible adverse effects on the environment, public health or the market economy. However, as the GMOs will be developed within approved containment facilities which have structural requirements and operational procedures to prevent the escape of the GMOs, I consider that it would be highly improbable that the GMOs will escape from containment.

Therefore I did not identify non-negligible adverse effects on the environment, public health or the market economy.

3.3. I did not identify non-negligible adverse effects on personnel handling the GMOs as exposure to the GMOs is voluntary and those personnel are trained to safely handle the GMOs.

3.4. I did not identify non-negligible adverse effects on society and community as:

- the GMOs will be developed within approved containment facilities which have structural requirements and operational procedures to prevent the escape of the GMOs, and
- the GMOs do not involve host organisms or genetic modifications that I consider will adversely affect society and community.

3.5. I did not identify non-negligible adverse effects on Māori and their culture and traditions with their ancestral lands, water, sites, waahi tapu, valued flora and fauna, and other taonga as:

- the GMOs will be developed within approved containment facilities which have structural requirements and operational procedures to prevent the escape of the GMOs.

4. The decision-making

4.1. I had sufficient information to assess the application as submitted by the applicant.

4.2. As per section 42A(3) of the Act, after completing a rapid assessment of adverse effects, I have decided to approve the application and impose controls providing for each of the matters specified in Schedule 3 as I think fit.

4.3. The matters to be addressed by containment controls for developing GMOs are listed in Part 1 of Schedule 3 of the Act. To address these, controls must be imposed to:

- limit the likelihood of any accidental release of any organism or any viable material
- exclude unauthorised people from the facility
- exclude other organisms from the facility and control undesirable and unwanted organisms within the facility
- prevent the unintended release of the organisms by researchers working with the organisms
- control the effects of any accidental release or escape of the organisms, and
- specify inspection and monitoring requirements for the containment facilities.

4.4. I imposed the controls detailed in Table 2 to provide for the matters above and any other matters I considered necessary to give effect to the purpose of the Act.

4.5. I note that the applicant has detailed their containment regime in section 4.2 of the application. I consider that this containment regime is adequate, since the genetic modifications will be carried out at MPI-approved facilities registered to at least a PC2 standard.

Table 2: Controls

The approval holder must ensure compliance with the following controls.	
1)	This approval is limited to the development of the GMOs described in Table 1 and the Schedule ("approved organisms") to undertake genetic modification of cell lines from humans to enable the packaging of 3rd generation self-inactivating lentiviral vectors and the creation of Chimaeric Antigen Receptor T cells.
2)	The approved organisms must not escape containment.
3)	The approved organisms must be developed within a containment facility that complies with: • The MAF/ERMA New Zealand Standard: Facilities for Microorganisms and Cell Cultures[2]: 2007a • The Australian/New Zealand Standard AS/NZS 2243.3:2002 Safety in laboratories: Part 3: Microbiological aspects and containment facilities[3], and • Physical Containment level 2 (PC2) requirements of the above Standards (at minimum) for developments involving the efficient disruption of specific endogenous genes or the precise modification of endogenous sequences in cultured human cell lines.
4)	The approval holder must ensure that within 24 hours of the discovery of any breach of containment (includes the escape of an organism(s) or a failure in the structural integrity of physical containment), the Ministry for Primary Industries biosecurity inspector responsible for supervision of the facility, has received notification (written or verbal)[4] of the breach and the details of any remedial action taken.

4.6. The applicant is not, in this instance, required to provide progress reports as this application does not raise any novel issues.

4.7. I have not imposed an expiry date on this approval.

[2] Any reference to MAF/ERMA New Zealand or AS/NZS Standards in these controls also refers to any subsequent version approved or endorsed by the EPA.

[3] Any reference to MAF/ERMA New Zealand or AS/NZS Standards in these controls also refers to any subsequent version approved or endorsed by the EPA.

[4] The biosecurity inspector's contact details can be found in the facility containment manual.

5. Summary of the decision

5.1. Application APP204075, to develop in containment GMOs (as described in Table 1 and the Schedule of this decision), is **approved, with controls** under section 42A(3) (as described in Table 2 of this decision). This decision was based on the information supplied by the applicant and was considered in accordance with section 42A of the Act, the Regulations, and the Methodology.

	21/08/2020
Siobhan Quayle **Group General Manager, Regulatory Systems and Operations**	**Date**

Schedule: List of organisms, risk categorisations and genetic modifications proposed for development under APP204075

Organism	Approval number
Human (*Homo sapiens* L 1758) viral vector packaging cell lines, leukaemia cell lines and human patient-derived primary T cell lines	GMD102668