Australian Government
Department of Health
Office of the Gene Technology Regulator

Licence for dealings involving an intentional release of a GMO into the environment

Licence No.: DIR 183

Licence holder: The Westmead Institute for Medical Research

Clinical trial with genetically modified *E.coli* to reduce antibiotic resistance

Issued: 20 July 2021

Gene Technology Regulation in Australia

Australia's gene technology regulatory system operates as part of an integrated legislative framework. The *Gene Technology Act 2000* (Cth) and corresponding state and territory legislation form a substantial part of a nationally consistent regulatory system controlling the development and use of genetically modified organisms.

This licence is issued by the Gene Technology Regulator in accordance with the *Gene Technology Act 2000* and, as applicable, Corresponding State law.

The Gene Technology Regulator is required to consult with, and take into account advice from, a range of key stakeholders, including other regulatory authorities, on risks to human health and safety and to the environment in assessing applications for dealings involving the intentional release of genetically modified organisms into the Australian environment.

Other agencies that also regulate genetically modified organisms or GM products include Food Standards Australia New Zealand, Australian Pesticides and Veterinary Medicines Authority, Therapeutic Goods Administration, Australian Industrial Chemicals Introduction Scheme and the Department of Agriculture, Water and the Environment. Dealings conducted under any licence issued by the Regulator may also be subject to regulation by one or more of these agencies. It is recommended that the licence holder consult the relevant agency (or agencies) about their regulatory requirements.

The licence authorises the licence holder and persons covered by the licence to conduct specified dealings with the genetically modified organism(s) listed in Attachment A of this licence.

Further information on licence DIR 183

More information about the decision to issue this licence is contained in the Risk Assessment and Risk Management Plan prepared in connection with the assessment of the application for the licence. This document can be obtained from the Office of the Gene Technology Regulator (OGTR) website or by telephoning the Office on 1800 181 030.

CONDITIONS OF THIS LICENCE

1. In this licence:

    (a) unless defined otherwise, words and phrases used in this licence have the same meaning as they do in the Act and the Regulations;

    (b) words denoting a gender include any other gender;

    (c) words in the singular include the plural and words in the plural include the singular;

    (d) words denoting persons include a partnership and a body whether corporate or otherwise;

    (e) references to any statute or other legislation (whether primary or subordinate) are a reference to a statute or other legislation of the Commonwealth of Australia as amended or replaced from time to time and equivalent provisions, if any, in corresponding State law, unless the contrary intention appears;

    (f) where any word or phrase is given a defined meaning, any other part of speech or other grammatical form in respect of that word has a corresponding meaning;

    (g) specific conditions prevail over general conditions to the extent of any inconsistency.

2. In this licence:

'Act' means the *Gene Technology Act 2000* (Commonwealth) or the corresponding State Law under which this licence is issued.

'Analytical facility' means a laboratory in Australia accredited to undertake testing of human diagnostic Samples, such as a medical testing laboratory accredited by the National Pathology Accreditation Advisory Council (NPAAC), and conforming to the AS/NZS 2243.3:2010 Safety in Laboratories: Microbiological Safety and Containment, particularly in relation to the handling of human diagnostic specimens.

'Clinical trial site' means a medical facility in Australia such as a clinical trial facility and associated pharmacy, which are notified in writing to the Regulator for the purposes of conducting this clinical trial.

'Contingency Plan' means a written plan detailing measures to be taken if certain events, as specified in Condition 36, occur.

'Decontaminate' (or ***'Decontamination'***) means, as the case requires, kill the GMOs by one or more of the following methods:

a) chemical treatment;

b) autoclaving;

c) high-temperature incineration; or

d) a method approved in writing by the Regulator.

Note: 'As the case requires' has the effect that, depending on the circumstances, one or more of these techniques may not be appropriate.

'External service provider' means a person engaged by the licence holder solely in relation to transport, storage and/or disposal of the GMOs, or Sample analysis other than at a Clinical trial site, and who is not undertaking any dealings with the GMOs that are not for those purposes.

'GM' means genetically modified.

'*GMO'* means the genetically modified organisms that are the subject of the dealings authorised by this licence.

'NLRD' is a Notifiable low risk dealing. Dealings conducted as an NLRD must be assessed by an institutional biosafety committee (IBC) before commencement and must comply with the requirements of the Gene Technology Regulations 2001.

'OGTR' means the Office of the Gene Technology Regulator.

'Personal information' has the same meaning as in the *Privacy Act 1988*. Personal information means information or an opinion about an identified individual, or an individual who is reasonably identifiable:

(a) whether the information or opinion is true or not; and

(b) whether the information or opinion is recorded in a material form or not.

'Pharmacy' means a location within the Clinical trial site, where authorised staff stores, prepares, and dispenses medications in medical environment.

'Regulator' means the Gene Technology Regulator.

'*Regulations'* means the *Gene Technology Regulations 2001* (Commonwealth) or the corresponding State Law under which this licence is issued.

'Sample' means any biological material collected from an inoculated trial participant for analysis as part of the trial, and which may reasonably be expected to contain GMOs.

'Serious adverse event' means any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening;
- requires inpatient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- is a medically important event or reaction.

Section 1 General conditions and obligations

Holder of licence

3. The licence holder is The Westmead Institute for Medical Research.

Remaining an accredited organisation

4. The licence holder must, at all times, remain an accredited organisation.

Validity of licence

5. This licence remains in force until it is suspended, cancelled or surrendered. No dealings with the GMO are authorised during any period of suspension, or after the licence has been cancelled or surrendered.

Note: Although this licence has no expiry date, the duration of administration of the GMOs is restricted in accordance with Condition 23.

Persons covered by the licence

6. The persons covered by this licence are the licence holder, and any employees, agents or External service providers of the licence holder, or the project supervisor(s), or other persons who are, or have been, engaged or otherwise authorised by the licence holder or the project supervisor to conduct any of the dealings authorised by this licence.

7. To the extent that any activity by a trial participant may be considered to be a dealing for purposes of the Act, that dealing is authorised by this licence.

8. The licence holder must keep a record of all persons covered by this licence, and must keep a record of the contact details of the project supervisor(s) for the licence.

Note: Where External service providers are used, it is sufficient to record the company name and the position or job title of the person(s) conducting the dealing.

9. The licence holder must provide information related to the persons covered by the licence when requested to do so in writing by the Regulator and must provide the information within a time period stipulated by the Regulator.

Description of GMOs covered

10. The GMO covered by this licence is a GM *E.coli,* carrying the 2 curing plasmids pJIMK46 or pJIMK56, as described in Attachment A of the Licence.

Dealings authorised by this licence

11. The dealings authorised by this licence are to:

    (a) Conduct experiments with the GMO

        i) administer of the GMO to clinical trial participants

        ii) collect and analyse the GMO

    (b) transport from the clinical trial site to the site of analysis

    (c) dispose of the GMO

and the possession (including storage), supply and use the GMO for the purposes of, or in the course of, any of these dealings.

Note: In accordance with Condition 28, dealings with participant Samples and other materials are not subject to conditions of this licence if they are reasonably expected not to contain the GMOs.

12. Supply of the GMO for the purposes of dealings by a person or organisation not covered by this licence is only authorised by this licence if the Regulator provides prior written approval to the licence holder.

Note: For approval to be granted, the receiving person or organisation must have an appropriate authorisation to conduct dealings with the GMOs. This is likely to be an NLRD or a licence issued by the Regulator.

Conditions imposed by the Act

Note: The Act mandates the following 3 conditions.

Informing people of licence conditions (section 63)

13. The licence holder must inform any person covered by this licence, to whom a particular condition of the licence applies, of the following:

    (a) the particular condition (including any variations of it); and

    (b) the cancellation or suspension of the licence; and

    (c) the surrender of the licence.

Note 1: No particular conditions of this licence apply to trial participants; therefore Condition 13 does not apply to trial participants.

Note 2: No particular conditions of this licence apply to persons processing participant Samples; therefore, Condition 13 does not apply to those persons. However, under Condition 29, the licence holder must ensure that all dealings are conducted in a manner that maintains containment of the GMOs.

Monitoring and audits (section 64)

14. If a person is authorised by this licence to deal with the GMOs and a particular condition of this licence applies to the dealing by that person, the person must allow the Regulator, or a person authorised by the Regulator, to enter premises where the dealing is being undertaken, for the purposes of auditing or monitoring the dealing.

Additional information to be given to the Regulator (section 65)

15. The licence holder must inform the Regulator if he or she:

    (a) becomes aware of additional information about any risks to the health and safety of people, or to the environment, associated with the dealings authorised by the licence; or

    (b) becomes aware of any contraventions of the licence by a person covered by the licence; or

    (c) becomes aware of any unintended effects of the dealings authorised by the licence.

Note: For the purposes of this Condition:

(a) The licence holder is taken to have become aware of additional information if he or she was reckless as to whether such information existed; and

(b) The licence holder is taken to have become aware of contraventions, or unintended effects, if he or she was reckless as to whether such contraventions had occurred, or such unintended effects existed.

Informing the Regulator of any material changes of circumstance

16. The licence holder must immediately, by notice in writing, inform the Regulator of:

    (a) any relevant conviction of the licence holder occurring after the commencement of this licence;

    (b) any revocation or suspension after the commencement of this licence, of a licence or permit held by the licence holder under a law of the Commonwealth, a State, or a foreign country, being a law relating to the health and safety of people or the environment;

    (c) any event or circumstances occurring after the commencement of this licence that would affect the capacity of the licence holder to meet the conditions in it.

17. The licence holder must provide information related to the licence holder's ongoing suitability to hold a licence when requested to do so in writing by the Regulator and must provide the information within a time period stipulated by the Regulator.

Further conditions with respect to informing persons covered by the licence

18. If a particular condition, including any variation of it, applies to a person with respect to any dealing the licence holder must not permit a person covered by this licence to conduct that dealing unless the person has been informed of the condition, including any variation of it.

19. If a particular condition, including any variation of it, applies to a person with respect to any dealing, other than to an External service provider, the licence holder must not permit a person covered by this licence to conduct that dealing unless:

    (a) the licence holder has obtained from the person a signed and dated statement that the person:

        i) has been informed by the licence holder of the condition and, when applicable, its variation; and

        ii) has understood and agreed to be bound by the licence conditions, or its variation; and

iii) has been trained by the licence holder in a manner which enabled them to safely conduct the dealings in accordance with the conditions of this licence.

20. The licence holder must notify all persons covered by the licence, from whom Personal information relevant to the administration and/or enforcement of the licence is collected by the licence holder, that such Personal information may be disclosed to the Regulator.

21. The licence holder must ensure that a copy of the licence is readily available to all persons covered by the licence, other than External service providers, who are conducting dealings with the GMO.

Note: The licence may be made available electronically

Section 2 Limits and control measures

Limits on clinical trials conducted under this licence

22. A maximum of 100 trial participants may be inoculated with the GMO under the licence.

23. The preparation and administration of the GMO must be completed within 5 years from the date of issuing of the licence.

Conditions about trial participants

24. The licence holder must notify each trial participant, from whom Personal information relevant to the administration and/or enforcement of the licence is collected by the licence holder, that such Personal information may be disclosed to the Regulator.

25. The licence holder must ensure that exclusion criteria used in selecting trial participants include (though are not limited to) the following persons:

    (a) pregnant women; and

    (b) breastfeeding women.

26. Before inoculating any trial participant with the GMOs, the licence holder must obtain written agreement from the trial participant that they would:

    (a) remain at the clinical trial site for a minimum of 4 days after the last administration of the GMO or earlier if two consecutive faecal samples are shown to be free of GMOs; and

    (b) agree to comply with the instructions provided by the licence holder, including practicing good hygiene following the treatment (frequent hand washing with soap or hand disinfectant), until two consecutive Samples are negative for the presence of the GMO; and

    (c) upon discharge from the hospital, agree to collect and return any Samples in containers provided by the licence holder according to the instruction provided prior to administration.

27. The licence holder must ensure all trial participants are provided with a supply of unbreakable containers and plastic bags appropriate for transporting samples back to the Clinical trial site once they are discharged from hospital. These containers must be labelled to indicate the contact details for the Clinical trial site; and that it contains GMOs.

Note: Unbreakable means able to withstand all reasonably expected conditions of storage and transport such as: the forces, shocks and impacts expected during handling; or changes of temperature, humidity or air pressure.

Conditions related to the conduct of the dealings

28. Conditions that apply to dealings with GMOs do not apply to Samples collected from trial participants, or other materials or waste, that are reasonably expected not to contain the GMO.

The licence holder must provide to the Regulator upon request, a written justification for this expectation.

29. The licence holder must ensure that dealings are only conducted in a manner which:

    (a) does not compromise the health and safety of people; and

    (b) minimises the exposure of persons conducting the dealings to the GMO, other than intended exposure of trial participants.

Note: The licence holder may achieve this by only engaging or otherwise authorising persons to conduct dealings who are required to adhere to appropriate standards and guidelines. For example standards developed by the National Pathology Accreditation Advisory Council for pathology practices, the Australian Guidelines for the Prevention and Control of Infection in Healthcare, Guidelines for Good Clinical Practice and the National Safety and Quality Health Service (NSQHS) Standards, or the behavioural requirements for dealings conducted in OGTR certified facilities.

Preparation and administration of the GMOs and collection of samples

30. Administration of the GMOs into human trial participants must not commence prior to approval by a Human Research Ethics Committee.

31. The following activities must occur within a Clinical trial site:

    (a) administration of the GMO to trial participants.

    (b) collection of faecal/rectal samples after administration of the GMO.

Note: Before any of these activities take place, the details of each Clinical trial site must have been notified to the Regulator in accordance with Condition 38.

Note 2: In accordance with Condition 28, dealings with participant Samples and other materials are not subject to conditions of this licence if they are reasonably expected not to contain the GMOs.

Work practices at Clinical trial sites

32. For the purposes of Condition 29, the work practices and behaviours within a Clinical trial site must include, but are not limited to, the following:

    (a) persons administering the GMO must wear personal protective equipment including a gown, gloves, mask and eye protection;

    (b) Administration of the GMO must be conducted by suitably qualified and trained medical staff;

Transport, storage and disposal of the GMOs

33. Unless covered by an NLRD, the licence holder must ensure that transport of the GMOs must only be for the purposes of, or in the course of, another dealing permitted by this licence, or for supply in accordance with condition 12.

34. The licence holder must ensure that all GMOs, and waste that arises during administration which is reasonably expected to contain the GMO are decontaminated:

    (a) prior to disposal, unless the method of disposal is also a method of (decontamination; and

    (b) before or upon suspension, cancellation or surrender of the licence, unless covered by another authorisation under the Act, or exported; and

    (c) by autoclaving, chemical treatment or high-temperature incineration;

35. For disposal by External service providers, the licence holder must ensure that the GMO, or waste reasonably expected to contain the GMO, enters the clinical waste stream for decontamination via autoclaving or high-temperature incineration.

Note: In the event of a spill during transport by an External service provider, compliance with relevant State or Territory legislation and regulations to manage clinical or biohazardous spills is sufficient

Contingency plans

36. The licence holder must ensure that any person (other than a trial participant) exposed to the GMOs is offered prompt medical advice. The clinician must be provided with any relevant information about the GMO, including any drugs to which it may be resistant.

37. If there is a spill or an unintentional release of GMO at the Clinical trial site, the following measures must be implemented:

    (a) the GMOs must be contained to prevent further dispersal; and

    (b) the exposed area must be decontaminated with an appropriate chemical disinfectant effective against the GMO; and

    (c) the licence holder must be notified as soon as reasonably possible.

Section 3 Notification and Reporting

*Note: Notices may be by email to OGTR.M&C@health.gov.au. A summary of notification and reporting requirements is provided at **Attachment B**.*

38. At least 14 days prior to first administering the GMO at each Clinical trial site, the licence holder must provide the Regulator with a Compliance Management Plan for that Clinical trial site, specifying:

    (a) the name, address and description of the Clinical trial site, including any associated pharmacies/storage areas/analytical facilities;

    (b) the key persons responsible for the management of the trial at the site;

    (c) that the Institutional Biosafety Committee (IBC) associated with the site (if any) has been notified of the trial;

    (d) the proposed reporting structure for the trial at the site and how the reporting structure enables the licence holder to become aware of any self-reported incidents for the purposes of Conditions 40(b) and 40(c);

    (e) details of how the persons covered by the licence (for that type of dealing) will be informed of licence conditions applicable to them and how they will be trained to safely conduct the dealings;

    (f) the person(s) or class of persons administering the GMO;

    (g) where, within the site, the GMO is expected to be administered;

    (h) the expected date of first administration;

    (i) transport and disposal procedures for the GMO and waste containing the GMO for the site; and

    (j) how compliance with Condition 28 will be achieved in relation to preparation of participant samples for analysis subsequent to administering the GMO.

Note: For the purpose of finding out whether the Act has been complied with, an OGTR inspector may, if entry is at a reasonable time, enter a facility occupied by the licence holder or a person covered by the licence and exercise monitoring powers.

39. The licence holder must notify the Regulator, in writing, of the final inoculation of the last trial participant at each Clinical trial site, within 30 days of the decision to cease the dealings.

40. The licence holder must inform the Regulator as soon as reasonably possible:

(a) in the event of a trial participant experiencing a Serious adverse event which may be related to the GMO;

(b) if they are notified of, or otherwise become aware of, a loss or spill of the GMO;

(c) if they are notified of, or otherwise become aware of, the exposure of a person other than a trial participant to the GMO; and

(d) if they become aware that a trial participant has not followed the procedures described in the instructions provided by the licence holder.

41. Upon request from the Regulator, the licence holder must provide any signed records or documentation collected under a condition of this licence, within a time period stipulated by the Regulator.

Attachment A

DIR No: 183

Full Title: Clinical trial with genetically modified *E.coli* to reduce antibiotic resistance.

Organisation Details

Postal address: The Westmead Institute for Medical Research

176 Hawkesbury Rd,

Westmead,

New South Wales, 2145

Phone No: (02) 8627 3000

GMO Description

GMOs covered by this licence:

The GMO being administered, *Escherichia coli* (Nissle strain) has been modified by the insertion of two antibiotic resistance plasmids with deletions of genes that are responsible for resistance to multiple classes of antibiotics and persistence of plasmids in bacteria. In addition, genes encoding resistance to specific antibiotics (fosfomycin or tetracycline) for GMO selection were introduced into the GMO.

Human gut bacteria that acquires the modified plasmids from the modified *E.coli*.

Parent Organisms:

Common Name: *E. coli* and human gut bacteria.

Scientific Name: *Escherichia coli* (Nissle strain) and human gut bacteria.

Modified traits:

Categories: Human therapeutic – reduced antibiotic resistance in gut bacteria.

Description: The GMO administered to trial participants, is a modified *E.coli* that carries two plasmids, where genes encoding antibiotic resistance were removed and genes for the antibiotic selection of bacteria carrying these plasmids. The *E.coli* is then expected to transfer these plasmids to bacteria in the human gut. Human gut bacteria that has received these plasmids will then be selected with antibiotics (fosfomycin and tetracycline) resulting in human gut bacteria with reduced antibiotic resistance.

Table 1. Nucleic acid responsible for conferring the modified traits

Identity and modifications	Insert of two plasmids with deletions of genes responsible for: • Resistance to multiple classes of antibiotics *bla*IMP4, *blaCMV-2, qacG2, aacA4 and catB3* • Persistence of plasmid in bacteria *pndA, pndBC, peml* and *pemK* Introduction of antibiotic resistance genes: • *fosA3* • tetA
Function	Antibiotic resistance genes: • *bla*IMP4 – anti-Metallo-β-lactamase • *blaCMV-2* – anti-Extended Spectrum β-lactamase • *qacG2* – anti-multidrug efflux protein • *aacA4* - anti-Aminoglycoside (N6') – acetyltransferase type 1 • *catB3* – anti-Choramphenicol acetyltransferase Antibiotic persistence genes: • *pndA, pndBC, peml* and *pemK* – removes ability of plasmid to persist in bacteria. Antibiotic resistance gene for selection: • *fosA3* – anti-fosfomycin • tetA – anti-tetracyclin

Purpose of the dealings with the GMOs:

To conduct clinical trials assessing the safety and efficacy of a genetically modified *E.coli* to deliver genes to gut bacteria to restore its sensitivity to antibiotics.

Attachment B

Prior to the commencement of the trial	Condition	Timeframe
A Compliance Management Plan for each trial site, including: • the name, address and description of the Clinical trial site, including any associated Pharmacies/storage areas/analytical facilities; • the key persons responsible for the management of the trial at the site; • that the Institutional Biosafety Committee (IBC) associated with the site (if any) has been notified of the trial; • the proposed reporting structure for the trial at the site and how the reporting structure enables the licence holder to become aware of any self-reported incidents for the purposes of conditions 40 (b) and (c); • details of how the persons covered by the licence (for that type of dealing) will be informed of licence conditions applicable to them and how they will be trained to safely conduct the dealings; • the person(s) or class of persons administering the GMO; • where, within the site, the GMO is expected to be administered; and • transport and disposal procedures for the GMOs and waste containing the GMO for the site; and • expected date of first administration. • how compliance with Condition 28 will be achieved in relation to preparation of participant samples for analysis subsequent to administering the GMO	38	At least 14 days prior to first administration of the GMO at that particular Clinical trial site.
Information to be provided at any time during the Clinical trial		
Any additional information related to the health and safety of people and the environment associated with the dealing covered by the licence, or any unintended effect of the dealing authorised by the licence	15(a), (c)	As soon as the licence holder becomes aware
Information related to any contravention of the licence by a person covered by the licence	15(b)	As soon as the licence holder becomes aware
Any relevant conviction of the licence holder	16(a)	Immediately
Any revocation or suspension of a licence or permit held by the licence holder under a law of the Commonwealth, a State or a foreign country	16(b)	Immediately

Any event or circumstances that would impact the licence holder capacity to meet the licence conditions	16(c)	Immediately
Any Serious adverse event which may be related to the GMO	40(a)	As soon as reasonably possible
Any loss or spill of the GMO, or exposure of a person other than the trial participant to the GMO	40(b), (c)	As soon as reasonably possible after becoming aware of the event
Any event where a trial participant has not followed the procedures described in the instruction provided by the licence holder	40(d)	As soon as reasonably possible after becoming aware of the event
The final inoculation of the last trial participant at each Clinical trial site,	39	Within 30 days of the decision to cease the therapy.
Information to be provided on request by the Regulator		
Information related to the persons covered by the licence	9	Within a timeframe stipulated by the Regulator
Information related to the licence holder's ongoing suitability to hold a licence	17	Within a timeframe stipulated by the Regulator
Any signed records or documentation collected under a condition of this licence	41	Within a timeframe stipulated by the Regulator