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

Licence No: DIR 126

Licence holder: PaxVax Australia Pty Ltd (PaxVax)

Title: Clinical trial of a genetically modified vaccine against Cholera

Issued: 10 April 2014

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 website at <http://www.ogtr.gov.au/**>, or by telephoning the Office on 1800 181 030.**

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 (GMOs).

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 GMOs into the Australian environment.

Other agencies that also regulate GMOs or GM products include Food Standards Australia New Zealand, Australian Pesticides and Veterinary Medicines Authority, Therapeutic Goods Administration, National Industrial Chemicals Notification and Assessment Scheme, National Health and Medical Research Council and the Department of Agriculture. 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 B** of this licence.

Dealings permitted by this licence may also be subject to the operation of State legislation declaring areas to be GM, GM free, or both, for marketing purposes.

Section 1 Interpretations and Definitions

1. In this licence:

- unless defined otherwise in this licence, words and phrases used in this licence have the same meaning as they do in the Act and the Gene Technology Regulations 2001;
- words importing a gender include any other gender;
- words in the singular include the plural and words in the plural include the singular;
- words importing persons include a partnership and a body whether corporate or otherwise;
- 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;
- 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;
- specific conditions prevail over standard conditions to the extent of any inconsistency.

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

'**Annual Report**' means a written report provided to the Regulator within ninety (90) days of each anniversary of issue of this licence containing all the information required by this licence to be provided in the Annual Report.

'Dealings' in relation to a GMO, means the following:

a) conduct experiments with the GMO;

b) make, develop, produce or manufacture the GMO;

c) breed the GMO;

d) propagate the GMO;

e) use the GMO in the course of manufacture of a thing that is not the GMO;

f) grow, raise or culture the GMO;

g) import the GMO;

h) transport the GMO;

i) dispose of the GMO;

and includes the possession, supply or use of the GMO for the purposes of, or in the course of, a dealing mentioned in any of paragraphs (a) to (i).

'**Destroy**', (or '**Destroyed**' or '**Destruction**') means, as the case requires, killed by one or more of the following methods:

a) treatment with chemical disinfectant

b) autoclaving

c) incineration.

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

'GM' means genetically modified.

'GMOs' means the genetically modified organisms the subject of the dealings authorised by this licence.

'**ICH-GCP'** means the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, *Guidelines for Good Clinical Practice*.

'**Material'** means non-biological material used in conjunction with the GMO, such as syringes, swabs, vials, gloves or for clean-up of spills.

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

'Personal Information' means information or an opinion (including information forming part of a database), whether true or not, and whether recorded in a material form or not, about an individual whose identity is apparent, or can reasonably be ascertained, from the information or opinion.

'Regulator' means the Gene Technology Regulator.

'**Sample'** means any biological material collected from trial subjects for subsequent analysis.

'TGA GCP Guidelines' means the TGA *Note for Guidance on Good Clinical Practice* designated CPMP/ICH/135/95.

'Trial participant' means a person who receives the GMO as a vaccine, or the parent/carer of such a person.

'WHO Universal Precautions' means World Health Organisation *Universal precautions for the prevention of transmission of infectious agents in healthcare settings*.

Section 2 General conditions

2. This licence does not authorise dealings with GMOs that are otherwise prohibited as a result of the operation of State legislation declaring areas to be GM, GM free, or both, for marketing purposes.
3. This licence remains in force until it is suspended, cancelled or surrendered. No dealings with the GMO are authorised during any period of suspension.
4. The holder of this licence ('the licence holder') is PaxVax Australia Pty Ltd.
5. The licence holder must immediately notify the Regulator in writing if any of the contact details of the project supervisor change.
6. The persons covered by this licence are the licence holder and employees, agents or contractors of the licence holder and other persons who are, or have been, engaged or otherwise authorised by the licence holder to undertake any activity in connection with 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 only permitted dealings authorised by this licence are to:
    a) conduct experiments with the GMOs;

b) import the GMO;

c) transport the GMO;

d) dispose of the GMO;

and the possession, storage, supply and use of the GMOs in the course of any of these dealings.

9. The only permitted experiments are:

a) administration of the GMOs (via oral ingestion) to trial participants; and

b) collection of samples that may contain the GMOs from trial participants.

10. The permitted experiments may only be conducted between 10 April 2014 and 30 June 2015.

Obligations of the Licence Holder

11. The licence holder must, at all times, remain an accredited organisation in accordance with the Act and must comply with its instrument of accreditation.

Prior to issuing a licence, the Regulator considers suitability of the applicant to hold a licence. The following conditions address ongoing suitability of the licence holder.

12. The licence holder must:

a) inform the Regulator immediately in writing, of

i. any relevant conviction of the licence holder occurring after the commencement of this licence; and

ii. any revocation or suspension of a licence or permit held by the licence holder under a law of the Australian Government, a State or a foreign country, being a law relating to the health and safety of people or the environment; and

iii. any event or circumstances occurring after the commencement of this licence that would affect the capacity of the holder of this licence to meet the conditions in it; and

b) provide any information related to the licence holder's ongoing suitability to hold a licence, if requested, within the stipulated timeframe.

The following conditions seek to ensure that persons conducting the dealings are aware of the licence conditions and appropriate processes are in place to inform people of their obligations.

13. Prior to commencing the clinical trial with the GMOs at each site, the licence holder must provide to the Regulator:

a) names of all organisations and persons or functions or positions of the persons, other than trial participants, who will be covered by the licence, with a description of their responsibilities; and

Note: examples of functions or positions are 'Site manager', 'Clinical research assistant', 'couriers', 'clinical waste contractors' etc.

b) detail of how the persons covered by the licence will be informed of licence conditions; and

Note: this may include training, labelling, contractual agreements with other organisations such as contract research organisations, clinical waste treatment providers and courier companies, etc.

c) detail of how the licence holder will access and control all the sites and approved facilities for the duration of the licence; and

Note: this may include a description of any contracts, agreements, or other enforceable arrangements.

d) written methodology to reliably detect the GMOs and the genetic modifications; and

e) a Contingency Plan for the site as described in Condition 46.

14. Any changes to the information provided under the immediately preceding condition must be communicated in writing to the Regulator within fourteen (14) days of the changes occurring.

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

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

b) the cancellation or suspension of the licence;

c) the surrender of the licence.

Note: Currently no conditions under this licence apply to trial participants; therefore this condition does not apply to trial participants.

16. Information required under the immediately preceding condition may be provided to contractors who are engaged solely for the transport and/or disposal of the GMOs through labelling the outermost container of the GMOs.

17. Subject to the following condition, the licence holder must not permit a person covered by this licence to conduct any dealing unless:

a) the person has been informed of the licence conditions, including any variation of it; and

b) 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 licence conditions including any variation of it; and

ii. has understood and agreed to be bound by the licence conditions, or its variations.

Note: Currently no conditions under this licence apply to trial participants; therefore this condition does not apply to trial participants.

18. The licence holder is not required to comply with any part of paragraph (b) of Condition 17 in relation to persons transporting the GMOs from the point of import to a trial site listed in Table 1 provided the consignment:

a) is clearly labelled to indicate (at a minimum) that it contains GMOs and is authorised under the *Gene Technology Act 2000* through DIR licence 126; and

b) is packaged and transported according to IATA requirements for class UN 3373; and

c) is only to be transported within Australia from the point of import to the trial site.

19. The licence holder is not required to comply with any part of paragraph (b) of Condition 17 in relation to persons transporting the GMOs (or waste containing GMOs) for the purpose of disposal through commercial clinical waste disposal methods provided:

    a) the GMOs are double contained; and

    b) the outermost container is labelled to indicate (at a minimum) that it contains GMOs which must be destroyed by autoclaving, chemical treatment, incineration or destroyed as clinical waste, along with contact details of the clinical trial site.

20. The licence holder must:

    a) inform the persons covered by this licence that any Personal Information relevant to the administration and/or enforcement of the licence may be released to the Regulator; and

    b) provide the Regulator, if requested, with copies of the signed and dated statements referred to in the condition listed in Condition 17.

Provision of new information to the Regulator

Licence conditions are based on the risk assessment and risk management plan developed in relation to the application using information available at the time of assessment. The following condition requires that any new information that may affect the risk assessment is communicated to the Regulator.

21. The licence holder must inform the Regulator, if the licence holder becomes aware of:

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

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

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

Note: The Act requires, for the purposes of the above condition, that:

    a) the licence holder will be 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 will be 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.

22. If the licence holder is required to inform the Regulator under the immediately preceding condition, the Regulator must be informed as soon as practically and reasonably possible.

Obligations of persons covered by the licence

23. Persons covered by this licence must not deal with the GMOs except as expressly permitted by this licence.

24. 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.

Section 3 Limits and control measures

Note: This licence does not expressly authorise or prohibit any dealings or storage in certified physical containment facilities. Under the Act it is not an offence to deal with a GMO if the dealing is otherwise licensed or if it is an NLRD or an exempt dealing and it complies with all relevant statutory requirements.

Limits on the release

The following licence conditions maintain the risk assessment context within which the application was assessed by imposing limits on where and when experiments with the GMOs may be performed, and on other activities that can be undertaken.

25. The GMO covered by this licence is PXVX0200, described in **Attachment A** of the licence.

26. Experiments with the GMOs must only be carried out at the clinical facilities listed in Table 1.

Table 1 Clinical facilities at which permitted dealings may occur.

Clinical Facility	Local Government Area	Locality
AusTrials Pty Ltd	City of Brisbane	Sherwood, QLD
QPharm Pty Ltd	City of Brisbane	Herston ,QLD
Cmax Australia Ltd	City of Adelaide	Adelaide, SA
Emeritus Research Pty Ltd	City of Stonnington	Malvern East, VIC
Nucleus Network	City of Banyule	Heidelberg, VIC
Nucleus Network	City of Melbourne	Melbourne, VIC
Royal Children's Hospital	City of Melbourne	Parkville, VIC
The University of Melbourne	City of Melbourne	Carlton, VIC
Linear Clinical Research Ltd	City of Nedlands	Nedlands, WA

27. The GMOs may be stored in a restricted access location at each clinical trial facility in Australia. Access to the storage location must be restricted to persons covered by the licence.

28. A maximum of 1000 trial participants are to be inoculated with the GMOs.

Controls on the Release

The following licence conditions maintain the risk assessment context within which the application was assessed by restricting exposure to the GMOs.

29. The trial must be conducted according to the TGA GCP Guidelines and WHO Universal Precautions.

30. The following persons must not be enrolled as trial participants:

    a) persons who have travelled to a cholera endemic area in the previous 5 years;

    b) persons who have abnormal stool patterns or regularly use laxatives;

c) persons who are allergic to tetracycline and/or ciprofloxacin;

d) persons who have a history of cholera or enterotoxigenic *E. coli* challenge;

e) pregnant or nursing women;

f) children less than two years of age; and

g) immunodeficient or immunosuppressed persons (by disease or therapy), including those with HIV infection.

31. Medical staff with the following conditions must be excluded from working with PXVX0200, or with trial participants who were inoculated with PXVX0200 in the previous 21 days:

a) pregnant or nursing women; and

b) immunodeficient or immunosuppressed persons (by disease or therapy), including those with HIV infection.

32. When preparing and administering the PXVX0200 vaccinations, medical staff must:

a) wear personal protective equipment including a laboratory coat and gloves; and

b) remove gloves and wash hands at the end of the procedure or after any potential exposure to the GMO.

33. All vaccinations must be administered orally (as a 100 ml liquid suspension to drink) by suitably qualified and trained medical staff.

34. The licence holder must ensure that trial participants receive a "patient supply kit" that includes:

a) detailed instruction on hygiene practices; and

b) instructions for parents/caregivers of child participants to:

- only use disposable nappies, and
- enclose used nappies in two sealed plastic bags prior to disposing as household waste for 21 days following vaccination.

Work practices

35. When undertaking a dealing with a GMO permitted by this licence, including storage, persons covered by this licence must employ work practices and behaviours which:

a) ensures containment of the GMO within the clinical facilities and during import, transport and disposal of the GMO; and

b) do not compromise the health and safety of people.

Containment measures

36. All dealings permitted under this licence must be conducted within clinical facilities listed in Table 1, except for:

a) import;

b) transport; and

c) disposal.

37. The GMOs may only be stored at a clinical trial facility listed in Table 1.

38. The GMO must be stored under two levels of containment. The outer most container must be unbreakable and clearly labelled to indicate that it contains GMOs.

    Note: In the case of a small storage unit such as a fridge, freezer or liquid nitrogen container, the secondary container may be the storage unit.

39. Access to the GMOs must be restricted to persons covered by the licence.

Section 4 Transport and Disposal

40. Transport of the GMOs, other than transport of the type listed in Condition 18, 19 and 44, must be in accordance with Part 1.2 of the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* as current at the time of transportation. Routes, methods and procedures used for transport (other than transport wholly within a building) must be documented and provided to the Regulator on request.

    Note: Part 1.2 of the Regulator's Guidelines for the Transport, Storage and Disposal of GMOs *requires that GM microorganisms are contained within two levels of unbreakable sealed containers. This is applicable when the transport is wholly within a building (e.g. transport from the storage location to the clinic).*

41. Before the expiration of this licence, all GMOs or any material or waste containing GMOs, must be destroyed by autoclaving, chemical treatment, incineration or any other method approved in writing by the Regulator. GMOs may be destroyed during or at the completion of the clinical trial.

42. For purposes of Condition 41, destruction may occur through commercial clinical waste disposal methods. Prior to disposal as clinical waste:

    a) the GMOs or any material or waste containing GMOs must be double contained; and

    b) the outermost container must be labelled to indicate that it contains GMOs and that it must be destroyed by autoclaving, chemical treatment, incineration or destroyed as clinical waste, along with contact details of the clinical trial site.

Section 5 Samples containing the GMO

43. Where a sample taken from a trial participant contains GMOs, or may reasonably be expected to contain GMOs, the sample may be collected and/or stored at locations other than clinical facilities but otherwise must be treated as if they were the GMO.

44. Any sample potentially containing GMOs that is collected for subsequent analysis must be transported according to Part 1.2 of the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* as current at the time of transportation.

Section 6 Reporting and Documentation Requirements

Contingency Plans

45. Prior to commencing any dealings authorised by this licence, a written Contingency Plan must be submitted to the Regulator detailing measures to be taken in the event of:

    - an unintentional release of GMOs such as a spill of GMOs outside the facilities listed in Table 1, during storage, transport or disposal, or
    - if persons other than trial participants are exposed to the GMOs, or

- in the case of a severe adverse event.

46. The Contingency Plan must include details of procedures to:

    a) ensure the Regulator is notified immediately if the licence holder becomes aware of the event; and

    b) implement the following measures if there is a spill of the GMO, such as during import, transport, storage, or disposal:

        i. the GMOs must be contained to prevent further dispersal; and

        ii. the exposed area must be decontaminated with an appropriate chemical disinfectant effective against the GMOs; and

    c) provide medical treatment to persons other than trial participants as necessary if they are exposed to the GMOs;

    d) provide medical treatment as necessary in the case of a severe adverse event; and

    e) implement the following measures if the GMO is transmitted to people other than trial participants:

        i. identify the pathway of exposure;

        ii. prevent the further spread or persistence of the GMO; and

        iii. provide medical treatment to affected persons as necessary.

47. The contingency plan must be implemented as soon as reasonably possible following the occurrence of any of the events listed in Condition 45.

Notice of commencement and completion of the trial

48. The licence holder must notify the Regulator in writing within thirty (30) days of vaccine administration to the first trial participant at each site.

49. The licence holder must notify the Regulator in writing within thirty (30) days of vaccine administration to the last trial participant at each site.

Annual Report

50. The licence holder must provide an Annual Report to the Regulator that includes:

    a) the number of trial participants inoculated with the GMOs under this licence in the previous twelve (12) months; and

    b) details of any significant adverse events linked to exposure to the GMOs.

Testing methodology

51. The licence holder must provide written documentation to the Regulator describing an experimental method that is capable of reliably detecting the presence of the GMO and the presence of the genetic modifications described in this licence in a recipient organism. The detection method should be capable of reliably distinguishing between the GMO described in this licence and the parent organism. The document must be provided prior to commencing any dealings authorised by this licence.

ATTACHMENT A

DIR No: 126

Full Title: **Clinical trial of a genetically modified vaccine against Cholera**

Organisation Details

Postal address: PaxVax Australia Pty Ltd (PaxVax)
Level 10
167 Eagle Street
BRISBANE 4001 QLD

Phone No: (03) 97875564, 0408109548

IBC Details

IBC Name: IBC 1033 (Queensland Clinical Trials Network Inc IBC)

ATTACHMENT B

GMO Description

The bacteria that causes cholera (*Vibrio cholerae*) has been genetically modified to remove its ability to cause disease. The modifications were: deletion of the genes encoding the cholera toxin A-subunit (leading to attenuation); inactivation of the gene encoding haemolysin A (also leading to attenuation); and insertion of a mercury resistance operon from *Shigella flexneri* (as a selectable marker). The GM cholera vaccine is currently known as PXVX0200.

Parent Organism:

Common Name: Cholera bacterium

Scientific Names: *Vibrio cholerae* strain 569B

Modified traits:

Categories: Loss of toxin expression/ Vaccine attenuation

Gene inactivation/ Vaccine attenuation

Selectable marker expression

Description:

- deletion of *Cholera toxin A subunit* gene (*ctxA*) (loss of toxin expression - vaccine attenuation)
- inactivation of *haemolysin A* gene (*hlyA*) (loss of toxin expression - vaccine attenuation)
- insertion of mercury resistance operon (*mer*) from *Shigella flexneri* NR1 (selectable marker – mercury resistance)

Purpose of the dealings with the GMOs:

PaxVax Australia will be conducting a clinical trial of a genetically modified cholera vaccine involving volunteers covering different age groups. This trial would form part of an international clinical trial and would involve up to 1000 participants in Australia. The purpose of the trial is to verify the effectiveness of the vaccine in producing an immune response against cholera.

Genetic elements responsible for conferring the modified traits:

Gene	Full name	Function of protein	Intended purpose
ctxA	*Cholera toxin A subunit* gene	deletion of *Cholera toxin A subunit*	vaccine attenuation
hlyA	*haemolysin A* gene	inactivation of *haemolysin A* gene	vaccine attenuation
mer Operon	mercury resistance operon from *Shigella flexneri* NR1	confers mercury resistance	selectable marker