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

Licence No: DIR 116

Licence holder: PPD Australia Pty Ltd

Title: Limited and Controlled Release of Genetically Modified Live Viral Vaccines Against Prostate Cancer

Issued: 5 October 2012

Varied: 11 June 2013

Updated: 18 June 2013

Varied: 8 August 2013

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, Fisheries and Forestry Biosecurity. 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:

   (a) unless defined otherwise in this licence, words and phrases used in this licence have the same meaning as they do in the *Gene Technology Act 2000* (the Act) and the Gene Technology Regulations 2001;

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

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

   (d) words importing 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 standard conditions to the extent of any inconsistency.

2. In this licence:

'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. Commercial clinical waste disposal methods are considered appropriate for the destruction of GMO waste created under this licence.

'GM' means genetically modified.

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

'IATA' means International Air Transport Association

'**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 cleaning 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.

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

Section 2 General conditions

3. 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.
4. This licence remains in force until 31 December 2017 unless it is suspended, cancelled or surrendered. No dealings with the GMOs are authorised during any period of suspension.
5. The holder of this licence ('the licence holder') is PPD Australia Pty Ltd.
6. The Project Supervisor in respect of this licence is a person named in **Attachment A** of this licence. The licence holder must immediately notify the Regulator in writing if any of the contact details of the project supervisor change.
7. 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.
8. 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.
9. The only 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.

10. The only experiments authorised by this licence are the:

(a) inoculation of trial participants with the GMOs; and

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

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.

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) name and location of the site at which the dealings are to occur

(b) 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' etc.

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

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

(d) written methodology to reliably detect the GMOs, the genetic modifications and distinguish between categories of GMOs approved for release; and

(e) Contingency Plan to respond to an unintentional release of GMOs such as a spill of GMOs outside the site, during storage, transport or disposal, or if persons other than trial participants are exposed to the GMOs.

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.

Information required under Condition 15 may be provided to contractors who are engaged for the transport of the GMOs through labelling the outermost container of the GMOs.

16. Subject to Condition 17, if a particular condition, including any variation of it, applies to a person with respect to a particular dealing, 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 them; 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 them; and

        (ii) has understood and agreed to be bound by the licence conditions, or any variation of them.

17. Where the GMOs are being transported within Australia, the licence holder is not required to comply with any part of paragraph (b) of Condition 16, provided the GMOs are transported as per Condition 38 for disposal or Condition 39 for purposes other than disposal.

18. 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 Condition 16.

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.

19. 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.

20. 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

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

22. 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.

23. The GMOs covered by this licence are PROSTVAC-V and PROSTVAC-F, described in **Attachment B** of the licence.

24. Experiments with the GMOs must only be carried out at clinical or pharmacy facilities (sites) located within the Australian Capital Territory and the Local Government Areas listed in Table 1.

Table 1 Local Government Areas in which permitted dealings may occur.

Local Government Areas	
City of West Torrens	City of Wodonga
Newcastle City Council	City of Stonnington
Greater Geelong City Council	City of Glen Eira
Brisbane City Council	City of Adelaide
Moreton Bay Regional Council	City of Yarra
City of Subiaco	City of Albury
The Council of the Shire of Hornsby	Banyule City Council
Tweed Shire Council	

25. The GMOs may be stored at Flinders Clinical Trials Services, Adelaide, South Australia, prior to distribution within Australia or export from Australia. Storage must be in

accordance with Part 2.1 of the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*, as current at the time of storage.

26. A maximum of 1200 male 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.

27. The trial must be conducted according to the ICH-GCP Guidelines as annotated by the Therapeutic Goods Administration, and WHO Universal Precautions.

28. Trial participants must previously have received a Smallpox vaccination containing *Vaccinia virus*.

29. Persons with the following medical conditions must not be inoculated with the GMOs:
    (a) persons with a history of, or active eczema or other eczematoid skin disorders;
    (b) persons with other acute, chronic or exfoliative skin conditions (e.g. burns, impetigo, chicken pox, severe acne or other open rashes or wounds);
    (c) immunodeficient or immunosuppressed persons (by disease or therapy), including those with HIV infection.

30. The licence holder must not enrol a trial participant who they have ascertained is likely to come into contact with individuals at risk from exposure to the GMO within 21 days after the initial (PROSTVAC-V) vaccination. Individuals at risk from exposure include but are not confined to:
    (a) persons with a history of, or active eczema or other eczematoid skin disorders;
    (b) persons with other acute, chronic or exfoliative skin conditions (e.g. burns, impetigo, chicken pox, severe acne or other open rashes or wounds) until the condition resolves;
    (c) pregnant or nursing women;
    (d) children less than three years; and
    (e) immunodeficient or immunosuppressed persons (by disease or therapy), including those with HIV infection.

31. Clinical staff with the following conditions must be excluded from working with PROSTVAC-V, or with trial participants who were inoculated with PROSTVAC-V in the previous three (3) weeks:
    (a) persons with a history of, or active eczema or other eczematoid skin disorders;
    (b) persons with other acute, chronic or exfoliative skin conditions (e.g. burns, impetigo, chicken pox, severe acne or other open rashes or wounds) until the condition resolves;
    (c) pregnant or nursing women; and
    (d) immunodeficient or immunosuppressed persons (by disease or therapy), including those with HIV infection.

32. When preparing and administering the initial (PROSTVAC-V) vaccinations, clinical staff must:
    (a) wear personal protective equipment including a laboratory gown, eye protection and gloves

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

33. All inoculations must be administered subcutaneously by suitably qualified and trained clinical staff.

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

    (a) detailed instruction on injection site care, hygiene practices and how to dispose of bandages and other materials that have come into contact with the PROSTVAC-V injection site; and

    (b) medical equipment including water-proof bandages, absorbent towelling and disposable gloves; and

    (c) sealable biohazard bags and instructions on the use of these bags for disposal of any bandages and other items that have come into contact with the PROSTVAC-V injection site; and

    (d) a sealable outer container to be used by the trial participant when returning the biohazard bags containing the PROSTVAC-V waste to the clinical site. A label, as described in Condition 38(b), must be provided for the outer container.

Note: For the purposes of this licence, the terms "patient" and "trial participant" have the same meaning.

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, during import, transport, storage 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 at clinical or pharmacy facilities (sites) located within the Australian Capital Territory and the Local Government Areas listed in Table 1, except for:

    (a) import;

    (b) storage;

    (c) transport; and

    (d) disposal.

37. Procedures must be in place to account for the contents of all vials containing GMOs imported into Australia under this licence. GMOs must be accounted for from import to destruction, and records must be provided to the Regulator on request.

Section 4 Transport and Disposal

38. Waste generated during the study, other than patient waste generated following the PROSTVAC-F inoculations, must be discarded into sealed, leak-proof bags or containers. Prior to disposal this waste must be:

    (a) double contained; and

(b) labelled to indicate 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.

Note: Waste includes used vaccine syringes and vials.

39. Where the GMO is being transported for purposes other than disposal, the packaging label outlined in **Attachment C** of this licence must be attached to the outermost container.

40. Transport of the GMOs, not including waste containing GMOs, must be carried out:

    (a) In accordance with IATA Packaging Provisions for Biological Substances, Category B, UN 3373; or

    (b) 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.

41. Routes, methods and procedures used for this transportation in accordance with this licence must be documented and provided to the Regulator on request.

42. Before the expiration of this licence, all persons covered by this licence, other than trial participants, must destroy all GMOs or any material or waste containing GMOs, with the exception of patient waste generated following the PROSTVAC-F inoculations, 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.

43. For purposes of Condition 42, transport and destruction may occur through commercial clinical waste disposal methods.

Section 5 Samples containing the GMO

44. 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.

45. 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, and stored in accordance with Part 2.1 of these Guidelines.

Section 6 Reporting and Documentation Requirements

Contingency Plans

46. Within thirty (30) days of the date of issue of this licence, and before any patient receives the initial PROSTVAC inoculation, a written Contingency Plan must be submitted to the Regulator detailing measures to be taken in the event of:

    (a) the unintended release of the GMOs, including exposure of, or transmission to, persons other than trial participants, or spills; and

Note: The contingency plan should detail actions to be taken in the event that a person other than a trial participant (i.e. a clinical or personal contact of a patient) displays symptoms of vaccinia infection.

(b) a person exposed to PROSTVAC-V developing a severe adverse response, including those resulting from exposure to *Vaccinia virus* such as eczema vaccinatum, progressive vaccinia, generalised vaccinia and postvaccinal encephalitis.

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

(a) ensure the Regulator is notified as soon as reasonably possible after the licence holder becomes aware of the event

(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 GMO

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

(i) provide medical treatment to affected persons as necessary; and

(i) prevent the further spread or persistence of the GMO; and

(ii) identify the pathway of exposure

(d) implement the following measures if a person exposed to PROSTVAC-V exhibits symptoms of a severe adverse response to vaccinia, as described in Condition 46(b):

(i) provide appropriate medical treatment; and

(ii) prevent the spread or persistence of the GMO, including the provision of quarantine facilities where bandaging is no longer sufficient or practical, for example with generalised vaccinia.

Notice of commencement and completion of the trial

48. The licence holder must notify the Regulator in writing within thirty (30) days of the first inoculation of a trial participant.

49. The licence holder must notify the Regulator in writing of the conclusion of the Australian arm of the trial as soon as reasonably possible.

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;

(b) details of any serious adverse events linked or potentially linked to exposure to the GMOs; and

(c) the percentage of trial participants worldwide, who developed a pustule/pock following inoculation with PROSTVAC-V in the previous twelve (12) months.

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 GMO described in this licence and the parent organism. The document must be provided within thirty (30) days of the issuing of this licence

ATTACHMENT A

DIR No: 116

Full Title: Limited and Controlled Release of Genetically Modified Live Viral Vaccines Against Prostate Cancer

Organisation Details

Postal address: PPD Australia Pty Ltd
Floor 9
5 Queens Road
Melbourne VIC 3004

Phone No: (03) 9804 5211

IBC Details

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

ATTACHMENT B

GMO Description

Vaccinia virus and *Fowlpox virus* genetically modified to express four human genes (as described in the table below). The GM vaccinia is currently known as PROSTVAC-V, and the GM fowlpox is PROSTVAC-F.

Parent Organism:

Common Name: Vaccinia and Fowlpox vaccines

Scientific Names: *Vaccinia virus* strain New York City Board of Health Vaccine (NYCBH)

Fowlpox virus strain POXVAC-TC

Modified traits:

Categories: Altered antigenic content

Altered immune response

Description: The two viral vaccines (PROSTVAC-V and PROSTVAC-F) have been genetically modified by the introduction of a gene encoding human *prostate-specific antigen* (PSA). The viruses have also been genetically modified to express genes encoding three human immunological molecules *B7.1* (CD80), *intercellular adhesion molecule-1* (ICAM-1 or CD54), and *leukocyte function-associated antigen-3* (LFA-3 or CD58).

Purpose of the dealings with the GMOs:

PPD Australia will be conducting a clinical trial of two genetically modified vaccines in men with prostate cancer. This trial in Australia would form part of an international clinical trial involving 1200 patients in approximately 22 countries. The purpose of the trial is to evaluate the effectiveness of the viral vaccines in treating prostate cancer.

Genetic elements responsible for conferring the modified traits:

Gene	Full name	Function of protein	Intended purpose
PSA	Prostate-Specific Antigen	Liquefies semen allowing sperm to swim freely	Elicit an immune response against tumour cells expressing PSA
B7.1 (CD 80)	-	Provides a costimulatory signal necessary for T cell activation and survival	Enhance the immune response to PSA
ICAM-1 (CD 54)	Intercellular Adhesion Molecule-1	Aids in the binding of an immune cell to an antigen presenting cell	Enhance the immune response to PSA
LFA-3 (CD 58)	Leukocyte Function-Associated Antigen-3	Increases adhesion between T cells and antigen presenting cell and is involved in the regulation of T cell responses	Enhance the immune response to PSA

ATTACHMENT C

Packaging Label

Study BNIT-PRV-301

Contains GMO

Sender: ALMAC Clinical Services

4204 Technology Drive, Durham, NC 27704, USA

Telephone Number: 001 919 479 8850

In the event of a spill, contact the local sponsor:

Local Sponsor: PPD Australia Pty Ltd

Level 9, 5 Queens Rd, Melbourne, Victoria, Australia 3004. Tel: +61 3 9804 5211

Caution: If this outer carton is damaged and a spill of its contents is suspected, this outer carton or its contents must not be handled without personal protective equipment (PPE). Spills must be cleaned up using 70% isopropyl alcohol, 70% ethyl alcohol, or 10% chlorine bleach.