



7 May 2012

**APPLICATION FOR LICENCE FOR INTENTIONAL RELEASE OF GMOs INTO THE ENVIRONMENT: Application No. DIR 116**

**SUMMARY INFORMATION**

<b>Project Title:</b>	Limited and controlled release of genetically modified live viral vaccines against prostate cancer <sup>1</sup>
<b>Applicant:</b>	PPD Australia Pty Ltd
<b>Common name of the parent organism:</b>	Smallpox vaccine Poxvirus vaccine for chickens
<b>Scientific name of the parent organism:</b>	<i>Vaccinia virus</i> strain New York City Board of Health Vaccine (NYCBH) <i>Fowlpox virus</i> strain POXVAC-TC
<b>Modified trait(s):</b>	Altered antigenic content Altered immune response
<b>Identity of the gene(s) responsible for the modified trait(s):</b>	<i>Prostate-specific antigen (PSA)</i> gene from humans ( <i>Homo sapiens</i> ) for altered antigenic content <i>B7.1 (CD80)</i> , <i>ICAM-1 (CD54)</i> and <i>LFA-3 (CD58)</i> genes from humans for altered immune response.
<b>Proposed Location(s):</b>	Health care facilities in ACT, NSW, QLD, SA, VIC and WA
<b>Proposed Release Size:</b>	1200 patients worldwide
<b>Proposed Release Dates:</b>	November 2012–December 2017

**Introduction**

The *Gene Technology Act 2000* (the Act) in conjunction with the *Gene Technology Regulations 2001*, an inter-governmental agreement and corresponding legislation that is being enacted in each State and Territory, comprise Australia's nationally consistent regulatory system for gene technology. Its objective is to protect the health and safety of people, and the environment, by identifying risks posed by or as a result of gene technology, and managing those risks by regulating certain dealings with genetically modified organisms (GMOs).

The Act establishes a statutory officer, the Gene Technology Regulator (the Regulator), to administer and make decisions under the legislation. The Regulator is supported by the Office of the Gene Technology Regulator (OGTR), an Australian Government regulatory agency located within the Health and Ageing portfolio.

The legislation sets out requirements for considering applications for licences for dealings with GMOs, including matters that the Regulator must take into account before deciding whether or

---

<sup>1</sup> The title of the licence application submitted by PPD Australia Pty Ltd is 'A Randomized, Double-blind, Phase 3 Efficacy Trial of PROSTVAC-V/F ± GM-CSF in Men With Asymptomatic or Minimally Symptomatic Metastatic, Castrate-Resistant Prostate Cancer'.

not to issue a licence. The Regulator's *Risk Analysis Framework*<sup>2</sup> outlines the assessment process that will be followed.

### **The application and the proposed dealings**

The Regulator has received an application from PPD Australia Pty Ltd for a licence for dealings involving the intentional release of genetically modified (GM) live viral vaccines into the Australian environment on a limited scale under controlled conditions.

PPD Australia Pty Ltd proposes to conduct a clinical trial involving two GM vaccine viruses containing human genes that when expressed are expected to induce an immune response to help kill prostate cancer cells. This proposed trial 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. The trial is proposed to take place in hospitals and health care facilities in ACT, NSW, QLD, SA, VIC and WA. Once underway the trial is expected to be completed within five years.

The applicant has proposed a number of control measures to restrict the spread and persistence of the GMOs and their introduced genetic material that will be considered in the assessment of this application, including:

- Inoculating a maximum of 1200 individuals worldwide with the GM vaccines
- Excluding subjects from the trial that may come into contact with individuals at risk for secondary transmission of the GM vaccines
- Requiring that inoculations be performed by trained nurses and/or physicians at health care facilities in accordance with standard universal precautions and ICH-GCP<sup>3</sup>
- Storing and transporting all GM vaccine, including any waste or samples containing the GM vaccines, in accordance with relevant regulations<sup>4</sup>
- Covering vaccination sites with a sterile dressing to prevent transmission and returning all used dressing to the health care facility for disposal
- Disposing of all waste in accordance with standard clinical waste disposal practices as required by the relevant local and state legislation

### **Confidential Commercial Information**

Some information, including details of the genetic construct used to create the GMOs and unpublished data from previous clinical trials are the subject of an application for declaration as Confidential Commercial Information (CCI) under section 185 of the Act that is currently under consideration. The confidential information will be made available to the prescribed experts and agencies that will be consulted on the Risk Assessment and Risk Management Plan (RARMP) for this application.

---

<sup>2</sup> The *Risk Analysis Framework* and further information on the assessment of licence applications is available from the Office of the Gene Technology Regulator (OGTR). Free call 1800 181 030 or at <<http://www.ogtr.gov.au>>.

<sup>3</sup> The international conference on harmonisation of technical requirements for registration of pharmaceuticals for human use, guidelines for good clinical practice

<sup>4</sup> OGTR *Guidelines for the Transport, Storage and Disposal of Genetically Modified Organisms*, IATA Transportation Regulations

## Parent organisms

The applicant has proposed to use two different viral vaccines (first *Vaccinia virus*, then *Fowlpox virus*) with the same genetic modifications. This sequence of vaccinations has been shown to result in a greater immune response than either of the vaccines given individually.

The first parent organism, *Vaccinia virus*, is exotic to Australia but has been used world wide as a vaccine to protect against smallpox infection. The vaccinia strain New York City Board of Health Vaccine (NYCBH or NYCBOH) was used as the parent organism to create the GMO. This strain was one of the vaccines used during the worldwide smallpox vaccination campaign and is also used in the current smallpox vaccine registered by the Therapeutics Goods Administration (TGA) for use in Australia.

The second parent organism, *Fowlpox virus*, is endemic to Australia and periodically infects commercial chicken flocks. The strain used as the parent organism has been licensed in the United States of America for use as a vaccine to protect poultry against Fowlpox. There are currently three live attenuated *Fowlpox virus* vaccines registered for use in poultry in Australia.

## The genetic modification and its effect

The two viral vaccines proposed for release (PROSTVAC-V and PROSTVAC-F) have been genetically modified by the introduction of a gene encoding human *prostate-specific antigen* (PSA), which is intended to act as an antigenic target for the immune response. This gene has been genetically modified to increase the ability of the prostate-specific antigen protein to stimulate an immune response.

The viruses have also been genetically modified to express genes encoding three human immunological molecules *B7.1* (CD80), *intracellular adhesion molecule-1* (ICAM-1 or CD54), and *leukocyte function-associated antigen-3* (LFA-3 or CD58). These molecules are intended to attract immune cells to the site of infection and stimulate the specific type of immune response necessary for the effective clearance of prostate cancer tumour cells. *Vaccinia virus* promoters will drive expression of all four introduced human genes.

After inoculation with the GM vaccines, the subsequent expression of the human genes in host cells will induce antibody and cell mediated immune responses against the *prostate-specific antigen* (PSA). This is intended to stimulate the immune system to attack and destroy cancer cells expressing PSA.

## Method of genetic modification

Both GM viral vaccines were created by infecting tissue culture cells with the parent virus and a plasmid encoding all four human genes flanked by genomic viral sequences. The genes were then incorporated into the virus genome through homologous recombination between the virus genome and the genomic sequences found on the plasmids.

## Previous releases of the same or similar GMOs

There has been no previous release of these GM viral vaccines in Australia. However, the Regulator has issued a number of Licences for dealings not involving an intentional release into the environment (DNIR) involving genetically modified *Vaccinia* and *Fowlpox viruses*.

## Suitability of Applicant

Section 43(2)(f) of the Act requires the Regulator to be satisfied regarding the suitability of the applicant to hold a licence as a pre-requisite for considering DIR applications. The matters to be

considered are outlined in section 58 of the Act and include capacity to meet the conditions of a licence, relevant convictions and revocation of a licence or permit held under law relating to the health and safety of people or the environment.

The Regulator has determined that PPD Australia Pty Ltd currently meets the suitability requirements and will verify this continues to be the case prior to making any decision regarding the issuing of a licence.

### **Other regulatory approvals**

The applicant has indicated that a Clinical Trial Notification will be submitted to the TGA. The applicant has also indicated that they will be applying to Department of Agriculture, Fisheries and Forestry Biosecurity (DAFF Biosecurity) for a permit to import the vaccines.

### **Consultation process for this DIR application**

**The Regulator has decided that the application qualifies as a limited and controlled release**, under section 50A of the Act. The principal purpose of the application is to enable the conduct of experiments and the applicant has proposed limits on the size and duration of the release and controls to restrict the spread and persistence of both the GMOs and their genetic material in the environment.

This means that the Regulator is not required to consult on the assessment of this application until after a consultation Risk Assessment and Risk Management Plan (RARMP) has been prepared in accordance with section 51 of the Act. In the interim, copies of the application are available on request from the OGTR. Please quote application number DIR 116.

The Regulator will seek comment on the consultation RARMP from the public as well as a wide range of experts, agencies and authorities including the Gene Technology Technical Advisory Committee, State and Territory Governments, Australian Government agencies and the Minister for the Environment. The RARMP will then be finalised, taking into account matters raised relating to risks to human health and safety and the environment, and form the basis of his decision whether or not to issue a licence.

At this stage, **the RARMP is expected to be released for comment in July 2012**. The public will be invited to provide submissions on the RARMP via advertisements in the media and direct mail to anyone registered on the OGTR mailing list. The RARMP and other related documents will be available on the OGTR website, or in hard copy from the OGTR.

If you have any questions about the application or the assessment process, or wish to register on the mailing list, please contact the OGTR at:

**The Office of the Gene Technology Regulator, MDP 54 GPO Box 9848 Canberra ACT 2601**

**Telephone: 1800 181 030 Facsimile: 02 6271 4202 E-mail: [ogtr@health.gov.au](mailto:ogtr@health.gov.au)**

**Website <http://www.ogtr.gov.au>**