



July 2009

**APPLICATION FOR LICENCE FOR INTENTIONAL RELEASE OF GMOs INTO THE ENVIRONMENT: Application No. DIR 097**  
**SUMMARY INFORMATION**

Project Title:	Limited and controlled release: Clinical trial of a candidate vaccine against <i>Human respiratory syncytial virus</i> and <i>Human parainfluenza virus</i> type 3 <sup>1</sup>
Applicant:	PPD Australia Pty Ltd
Common name of the parent organism:	Bovine Parainfluenza virus type 3
Scientific name of the parent organism:	<i>Bovine parainfluenza virus 3</i> (strain Kansas/15626/84)
Modified trait(s):	Altered antigenic profile
Identity of the gene(s) responsible for the modified trait(s):	<ul style="list-style-type: none"><li>• <i>Human parainfluenza virus 3</i> haemagglutinin-neuraminidase (HN) gene</li><li>• <i>Human parainfluenza virus 3</i> fusion protein (F) gene</li><li>• <i>Human respiratory syncytial virus</i> fusion protein (RSV F) gene</li></ul>
Proposed Location(s):	Hospital clinics in ACT, NSW, QLD, SA, VIC, WA
Proposed Release Size:	3 inoculations of $\leq 10^6 \log_{10}$ TCID <sub>50</sub> <sup>2</sup> delivered to 35 trial subjects
Proposed Release Dates:	2009 - 2010

## **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 the legislation 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 the requirements for considering applications for licences for dealings with GMOs and the matters that the Regulator must take into account before deciding whether, or not, to issue a licence. The Regulator's *Risk Analysis Framework*<sup>3</sup> outlines the assessment process that will be followed.

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<sup>1</sup> The title of the licence application submitted by PPD Australia is 'Clinical study MI-CP178 "A phase 1/2a, randomized, double-blind, placebo-controlled, dose-escalation study to evaluate the safety, tolerability, immunogenicity and vaccine-like viral shedding of MEDI-534, a live, attenuated intranasal vaccine against respiratory syncytial virus and parainfluenza virus type 3 in healthy 6 to < 24 month-old children and in 2 month old infants".'

<sup>2</sup> Median tissue culture infectious dose

<sup>3</sup> More 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>>.

## The application and the proposed dealings

The OGTR has received a licence application (DIR 097) from Pharmaceutical Product Development Australia Pty Ltd (PPD) for an intentional release of a genetically modified (GM) vaccine for prevention of selected childhood respiratory diseases into the Australian environment which qualifies as a limited and controlled release under section 50A of the Act.

The GM candidate vaccine is based on *Bovine parainfluenza virus* (bPIV) which has been modified to contain genes from two common childhood respiratory pathogens *Human parainfluenza virus* type 3 (hPIV) and *Human respiratory syncytial virus* (RSV). Expression of these genes is expected to elicit a protective immune response in vaccinated children. PPD is seeking approval to conduct a clinical trial of the GM vaccine in children to evaluate its safety and efficacy against these pathogens.

The trial is proposed to take place in hospitals in ACT, NSW, QLD, SA, VIC and WA and would involve a maximum of 35 children aged 2 – 24 months. Once underway the trial is expected to run for a 13 month period.

The applicant has proposed a number of control measures to restrict the dissemination and persistence of the GM vaccine that will be considered in the assessment of this application including:

- Inoculating a maximum of 35 individuals with the GM vaccine
- Excluding subjects from the trial that may come into contact with individuals at risk for secondary transmission of GM vaccine
- Requiring that inoculations be performed by trained nurses and/or physicians at clinical facilities in accordance with standard universal precautions and ICH-GCP<sup>4</sup>
- Storing and transporting all GM vaccine, including any waste or samples containing GM vaccine, in accordance with relevant regulations<sup>5</sup>
- Disposing of all waste in accordance with standard clinical waste disposal practices

## Confidential Commercial Information

Some details, including unpublished results from related clinical trials, aspects of the proposed clinical trial protocol and sequence data of the GM vaccine are the subject of an application for declaration of Confidential Commercial Information (CCI) under section 185 of the Act, which 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.

## Parent organism

The parent organism bPIV is an enveloped, negative sense RNA virus within the genus *Respirovirus*, subfamily *Paramyxovirinae*, family *Paramyxoviridae*, order *Mononegavirales*. In addition to bPIV3, the genus *Respirovirus* includes four other recognised viral species: *Human parainfluenza virus 1*, *Murine parainfluenza virus 1*, *Human parainfluenza virus 3* and *Simian virus 10*.

Bovine parainfluenza virus 3 is endemic in Australia and is ubiquitous among feedlot age cattle. On its own, infection with bPIV rarely results in significant disease. However, acute bPIV

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<sup>4</sup> The international conference on harmonisation of technical requirements for registration of pharmaceuticals for human use, guidelines for good clinical practice

<sup>5</sup> OGTR Guidelines for the Transport of Genetically Modified Organisms, IATA Transportation Regulations

infection may suppress the normal immune response, which can leave cattle susceptible to bacterial infection that can result in multifactorial diseases such as Bovine Respiratory Disease Syndrome.

Bovine parainfluenza virus 3 has a broad host range. In addition to cattle some replication has been observed in primates, hamsters, rats and neonatal ferrets after experimental infection. Furthermore clinical trials have demonstrated that bPIV3 has a limited capacity for replication in humans, with infection resulting in mild flu-like symptoms.

### **The genetic modifications and their effect**

The bPIV parent has been modified to include:

- the hPIV3 haemagglutinin-neuraminidase (HN) gene in place of the bPIV3 HN gene;
- the hPIV3 fusion protein (F) gene in place of the bPIV3 F gene; and
- the RSV fusion protein (RSV F) gene inserted into a non-coding region of the bPIV3 genome.

The effect of the genetic modifications is to create a bovine PIV3 virus in which the surface glycoproteins that mediate interactions with host cells and immune molecules have been replaced with those from hPIV3. The vaccine virion therefore consists of the bPIV3 core surrounded by the envelope derived from the host cell membrane, from which protrude the hPIV3 HN and F glycoproteins. When the virus replicates in a host cell RSV F glycoproteins are also produced, but these are not incorporated into the envelope of virions.

Infection with the GM vaccine and subsequent expression of viral genes in infected cells is expected to result in a lytic, sub-clinical infection that elicits humoral and cell mediated immune responses against the viral proteins (*ie.* hPIV HA and F, RSV F and bPIV core proteins). The purpose of the trial is to determine whether the candidate GM vaccine will protect vaccinated individuals against hPIV and RSV infection.

### **Method of genetic modification**

The genome of bovine PIV3 has been cloned into a DNA plasmid that can be maintained and replicated in transformed bacteria. The human HN and F genes were substituted for the bovine HN and F genes using standard sub-cloning techniques. Similarly the RSV F gene has been inserted into a non-coding spacer region within the bPIV3 genome using standard sub-cloning techniques. The modified virus can be recovered by transfection of mammalian cell lines with the plasmid, resulting in transcription of the RNA genome, translation of the viral proteins and assembly of virions.

### **Previous releases of the same or similar GMOs**

There has been no previous release of the GM vaccine in Australia. A clinical trial involving the GM vaccine is currently underway in the USA. Approval for the use of the GM vaccine in clinical trials is also being sought in Brazil, Canada, Chile, Finland, Germany, New Zealand, South Africa, Spain and UK.

### **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 relevant convictions, revocation of a licence or permit relating to the health and safety of people, and capacity to meet the conditions of the licence.

The Regulator has determined that PPD 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 clinical trial of the vaccine has been authorised by the Therapeutic Goods Administration (TGA) under the Clinical Trial Exemption (CTX) scheme.

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

The Regulator has made an assessment of whether the application should be considered as a limited and controlled release, under section 50A of the Act. As its principal purpose is to carry out a clinical trial, and the applicant has proposed limits on the number of participants in the trial and controls to restrict the dissemination and persistence of the GMO in the environment, **the Regulator has decided that the application qualifies as a limited and controlled release.**

This means that the Regulator is not required to consult on the assessment of this application until after a 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 097.

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 (including the TGA) and the Minister for the Environment, Water, Heritage and the Arts. 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 her decision whether or not to issue a licence.

At this stage, **the RARMP is expected to be released for comment in October 2009.** 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:

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