Australian Government
Department of Health and Ageing
Office of the Gene Technology Regulator

5 October 2012

TECHNICAL SUMMARY OF THE RISK ASSESSMENT AND RISK MANAGEMENT PLAN
FOR
APPLICATION NO. DIR 116
FROM
PPD AUSTRALIA PTY LTD

Introduction

The Gene Technology Regulator (the Regulator) has made a decision to issue a licence in respect of licence application (DIR 116) from PPD Australia Pty Ltd (PPD). The licence authorises dealings involving the limited and controlled release of genetically modified (GM) live viral vaccines against prostate cancer.

The *Gene Technology Act 2000* (the Act), the Gene Technology Regulations 2001 and corresponding state and territory law govern the comprehensive and highly consultative process undertaken by the Gene Technology Regulator (the Regulator) before making a decision whether or not to issue a licence to deal with a genetically modified organism (GMO).

The decision is based upon a Risk Assessment and Risk Management Plan (RARMP) prepared by the Regulator in accordance with requirements of the legislation. RARMPs apply the *Risk Analysis Framework* and are finalised following consultation with a wide range of experts, agencies and authorities, and the public[1].

The application

PPD has applied for a licence for dealings involving the intentional release into the Australian environment of two genetically modified (GM) vaccines for the treatment of prostate cancer on a limited scale and under controlled conditions.

The GM vaccines are based on *Vaccinia virus* vaccine strain New York City Board of Health (NYCBH) and *Fowlpox virus* vaccine strain POXVAC-TC, which have each been modified to contain the same four human genes. Expression of these genes is expected to induce immune responses against the *Prostate-Specific Antigen* (PSA) and to stimulate the immune system to attack and destroy cancer cells expressing PSA.

[1] More information on the process for assessment of licence applications to release a genetically modified organism (GMO) into the environment is available from the Office of the Gene Technology Regulator (OGTR) (Free call 1800 181 030 or at <http://www.ogtr.gov.au/>), and in the Regulator's *Risk Analysis Framework* (OGTR 2009) at <http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/riskassessments-1>.

The 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. 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 proposed a number of control measures to restrict exposure of non-trial participants to the GM virus. These controls have been considered during the evaluation of the application.

Confidential Commercial Information

Some details, including vector maps and unpublished results from related clinical trials have been declared Confidential Commercial Information (CCI) under section 185 of the Act. The confidential information was made available, in accordance with section 187 of the Act, to the prescribed experts and agencies consulted on the RARMP for this application.

Risk assessment

The risk assessment took into account information in the application (including proposed containment measures), relevant previous approvals and current scientific/technical knowledge. Advice relating to risks to human health and safety and the environment provided in submissions received during consultation on the RARMP was also considered. No new risks to people or the environment were identified from the advice received on the consultation RARMP.

Initially, potential pathways that might lead to harm to people or the environment as a result of gene technology are postulated (risk scenarios), and those that warrant detailed characterisation are determined. This process is described as risk identification.

Seven risk scenarios were postulated, including consideration of whether or not expression of the introduced genes could result in products that are toxic or allergenic to people or other organisms; alter characteristics that may impact on the disease burden due to the GM virus; or produce unintended changes in its characteristics. The opportunity for gene transfer to other organisms, and its effects if this were to occur, was also assessed.

A risk is only identified for further assessment when a risk scenario is considered to have some chance of causing harm. Pathways that do not lead to an adverse outcome, or could not reasonably occur, do not advance in the risk assessment process.

The characterisation of the seven risk scenarios in relation to both the seriousness and likelihood of harm, in the context of the control measures proposed by the applicant and considering both the short and the long term, did not give rise to any identified risks that required further assessment. The principal reasons for this include:

- Transmission to the environment of the two GM viruses via viral shedding during the trial will be minimised through:
    - the participant exclusion criteria; the route of inoculation (subcutaneous); bandaging of the injection site and appropriate training of both healthcare workers and patients (in the case of vaccinia); and
    - the nature of the virus (in the case of fowlpox).
- No increase in disease severity due to the introduction of the four human genes has been observed in previous clinical trials.
- The products of the four introduced genes are not expected to be toxic to humans or other animals, due to their widespread presence in the environment.

Risks to the health and safety of people, or the environment, from the proposed release of the GM virus into the environment are assessed to be negligible.

Risk management plan

Risk management is used to protect the health and safety of people and to protect the environment by controlling or mitigating risk. The risk management plan evaluates and treats identified risks, evaluates controls and limits proposed by the applicant, and considers general risk management measures. The risk management plan is given effect through licence conditions.

As none of the seven risk scenarios characterised in the risk assessment give rise to an identified risk that requires further assessment, the level of risk from the proposed dealings is assessed to be negligible. The Regulator's *Risk Analysis Framework* defines negligible risks as insubstantial, with no present need to invoke actions for their mitigation in the risk management plan. However, a range of licence conditions have been imposed to restrict exposure to the GMO, to limit the proposed trial size and locations proposed in the application, as these were important considerations in establishing the context for assessing the risks.

Licence conditions

The Regulator has imposed a number of licence conditions, including requirements to:

- limit the trial to a maximum of 1200 trial participants inoculated with the GM viruses at designated clinical facilities
- restrict exposure of at-risk individuals by specific exclusion criteria
- restrict trial participation to people who have previously received a vaccinia vaccination
- restrict the method of inoculation of GM Vaccinia to subcutaneous inoculation
- ensure that inoculations be performed by trained nurses and/or physicians at clinical facilities in accordance with standard universal precautions and ICH-GCP[2], and that appropriate personal protective equipment is worn.
- store and transport all GM vaccines in accordance with relevant regulations and guidelines[3]
- dispose of all waste generated in the clinic, as well as patient waste following GM Vaccinia inoculation, in accordance with standard clinical waste disposal practices.

Other regulatory considerations

Australia's gene technology regulatory system operates as part of an integrated legislative framework that avoids duplication and enhances coordinated decision making. The Regulator is responsible for assessing risks to the health and safety of people and the environment associated with the use of gene technology. However, dealings conducted under a licence issued by the Regulator may also be subject to regulation by other agencies that also regulate GMOs or GM products including Food Standards Australia New Zealand (FSANZ), Australian Pesticides and Veterinary Medicines Authority (APVMA), Therapeutic Goods Administration (TGA), National Industrial Chemicals Notification and Assessment Scheme (NICNAS) and Department of Agriculture, Fisheries and Forestry (DAFF) Biosecurity[4].

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[2] The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use, guidelines for good clinical practice, as annotated by TGA (http://www.tga.gov.au/industry/clinical-trials-note-ich13595.htm).

[3] The Gene Technology Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs;* IATA Transportation Regulations

[4] More information on Australia's integrated regulatory framework for gene technology is contained in the *Risk Analysis Framework* (OGTR 2009) available from the Office of the Gene Technology Regulator (OGTR). Free call 1800 181 030 or at <http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/riskassessments-1>.

TGA is responsible for human safety assessment of the participants in clinical trials. The applicant has notified the TGA of the trial. Each trial site will also notify the TGA through the Clinical Trial Notification (CTN) Scheme. The Regulator sought advice from TGA during the assessment of this licence application.

Identification of issues to be addressed for future releases

Additional information has been identified that may be required to assess an application for a large scale or commercial release of the GM vaccines, or to justify a reduction in containment conditions. This includes the potential shedding of GM vaccinia from trial subjects.

Conclusions of the RARMP

The risk assessment concluded that this limited and controlled release of GM vaccines to take place in hospitals in ACT, NSW, QLD, SA, VIC and WA, involving up to 1200 trial participants and expected to run for up to five years, poses negligible risks to the health and safety of people or the environment as a result of gene technology.

The risk management plan concluded that these negligible risks do not require specific risk treatment measures. However, licence conditions have been imposed to limit the trial in size, locations and duration, and to require controls in line with those proposed by the applicant, as these were important considerations in establishing the context for assessing the risks.