Australian Government
Department of Health
Office of the Gene Technology Regulator

10April 2014

Summary of the Risk Assessment and Risk Management Plan for Licence Application No. DIR 126

Decision

The Gene Technology Regulator (the Regulator) has decided to issue a licence for this clinical trial of a genetically modified (GM) vaccine. This clinical trial is a limited and controlled release application under the *Gene Technology Act 2000* (the Act). A science based Risk Assessment and Risk Management Plan (RARMP) for the application was prepared by the Regulator in accordance with requirements of the Act and corresponding state and territory legislation, and finalised following consultation with a wide range of experts, agencies and authorities, and the public. The RARMP concludes that the proposed clinical trial poses negligible risks to human health and safety and the environment.

The application

Application number	DIR 126
Applicant	PaxVax Australia Pty Ltd (PaxVax)
Project title	Clinical trial of a genetically modified vaccine against Cholera[1]
Parent organism	Cholera bacterium (*Vibrio cholerae*)
Introduced or modified genes and resulting modified traits	• 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)
Proposed locations	Clinical sites in Queensland, South Australia, Victoria and Western Australia
Proposed trial size	A maximum of 1000 volunteers covering different age groups are proposed to be enrolled for the clinical trial
Proposed trial dates	10 April 2014 – 30 June 2015
Primary purpose	To verify the effectiveness of the vaccine in producing an immune response against cholera

[1] The title of the licence application submitted by PaxVax is "Clinical development of a recombinant live oral cholera vaccine (PXVX0200)".

The GM vaccine contains live genetically modified *V. cholerae* bacteria. Unmodified cholera bacteria produce a toxin containing 2 subunits (A and B) and haemolysin (a protein which can break open blood cells). The vaccine strain has been produced by deleting most of the toxic *A subunit* gene (*ctxA*) and inserting a mercury resistance operon (*mer*) into the *haemolysin* gene (*hlyA*). As a result of the genetic modification the GMOs cannot produce the A-subunit of the cholera toxin molecule or haemolysin. The non-active B-subunit of the cholera toxin molecule is still synthesised but this protein does not cause disease or toxicity on its own.

The *mer* operon was inserted into the *hlyA* gene to allow easy and rapid differentiation between the GM cholera vaccine strain, and the wild-type toxin producing *V. cholerae*. The *mer* operon does not encode proteins that can produce, store or sequester mercury. There is no mercury associated with the vaccine.

The clinical trial will involve oral administration of the vaccine to volunteers (both children and adults) in Australia. This trial will form part of a larger international study including trials in the USA and Canada. The purpose of these trials is to verify the effectiveness of the vaccine in producing an immune response against cholera. The Australian trial will take place in clinical facilities in Queensland, South Australia, Victoria and Western Australia. Once underway the trial is expected to be completed within approximately one year, depending upon the availability of volunteers.

Medicines and other therapeutic goods for sale in Australia are required to be assessed for quality, safety and efficacy under the *Therapeutic Goods Act 1989* and must be included in the Australian Register of Therapeutic Goods. The Therapeutic Goods Administration (TGA) is responsible for administering this legislation. This clinical trial must also be conducted in accordance with the relevant TGA requirements.

Risk assessment

The risk assessment concludes that risks to the health and safety of people, or the environment, from the proposed release are negligible.

The risk assessment process considered how the genetic modification and activities proposed to be conducted with the GMOs might lead to harm to people or the environment. Risks were characterised in relation to both the seriousness and likelihood of harm, taking into account information in the application (including proposed limits and controls), relevant previous approvals and current scientific and technical knowledge. Both the potential short and long term harms were considered.

Credible pathways to potential harm that were considered included whether or not expression of the introduced genes or changes in gene expression due to gene deletions 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 Cholera bacterium (*V. cholera*); or produce unintended changes in bacterial characteristics. The opportunity for unintended exposure to the vaccine or the GM bacteria it contains, and for gene flow to other organisms was also considered. No new risks to people or the environment were identified from the advice received on the consultation RARMP.

The principal reasons for the conclusion of negligible risks are that the proposed limits and controls effectively contain the GMO and its genetic material and minimise exposure; the introduced genetic modifications are unlikely to cause harm to people or the environment; and genes similar to the introduced genes are common in the environment.

Risk management plan

The risk management plan concludes that risks posed by the proposed dealings can be managed so as to protect people and the environment by imposing conditions on the release.

Risk management is used to control or mitigate risk. The risk management plan evaluates and treats substantive 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 the level of risk is assessed as negligible, specific risk treatment is not required. However, as this is a limited and controlled release, the licence includes limits on the size, locations and duration of the release, as well as controls including administration of the GM vaccine by trained staff, exclusion of individuals who could be at risk of adverse effects, fully informing volunteers participating in the trial, appropriate containment and waste disposal provisions at the clinical site, destroying GM vaccine not required for further studies and transporting the GM vaccine in accordance with the Regulator's transport guidelines or other specific condition.