



Summary of the Risk Assessment and Risk Management Plan (Consultation Version) for Licence Application No. DIR 174

Introduction

The Gene Technology Regulator (the Regulator) has received a licence application (DIR 174) for import, transport, storage and disposal of a genetically modified (GM) cholera vaccine, Vaxchora[®], as part of its commercial supply as a human vaccine. These activities are classified as Dealings involving the Intentional Release (DIR) of genetically modified organisms into the Australian environment.

Before the GM vaccine can be used as a human vaccine, Bioelect must also obtain regulatory approval from the Therapeutic Goods Administration (TGA). Therapeutic goods for sale in Australia must be included in the Australian Register of Therapeutic Goods (ARTG) under the *Therapeutic Goods Act 1989*. The TGA would assess patient safety, quality and efficacy prior to including the GM vaccine on the ARTG. In addition, approval from the Department of Agriculture, Water and the Environment will also be required for import of the GM vaccine.

The Regulator has prepared a Risk Assessment and Risk Management Plan (RARMP) for this application, which concludes that the proposed supply of the GM cholera vaccine poses negligible risks to human health and safety and the environment. Licence conditions have been drafted for the proposed release. The Regulator invites submissions on the RARMP, including draft licence conditions, to inform the decision on whether or not to issue a licence.

The application

Application number	DIR 174
Applicant	Bioelect Pty Ltd (Bioelect)
Project title	Commercial supply of a genetically modified cholera vaccine, Vaxchora ^{®1}
Parent organism	<i>Vibrio cholerae</i> strain 569B
Introduced gene and modified trait	<ul style="list-style-type: none">• Deletion of <i>Cholera toxin A subunit</i> gene (<i>ctxA</i>) (loss of toxin expression - vaccine attenuation)• Inactivation of <i>haemolysin A</i> gene (<i>hlyA</i>) (loss of toxin expression - vaccine attenuation)• Insertion of mercury resistance operon (<i>mer</i>) from <i>Shigella flexneri</i> NR1 (selectable marker - to allow identification of GM strain)
Previous releases	<p>Commercial supply of the GM <i>V. cholerae</i> strain as a human vaccine (formerly known as Orochol[®]) was previously approved in Australia. The GMO described in this application is the same GM <i>V. cholerae</i> strain as previously approved GM cholera vaccine Orochol[®].</p> <p><u>Orochol[®]:</u></p> <ul style="list-style-type: none">• Commercial supply of the GM cholera vaccine, Orochol[®], as a human

¹ The title of the licence application submitted by Bioelect is “Commercial use of Vaxchora[®] for immunisation against cholera”.

	<p>vaccine was previously approved by the Genetic Manipulation Advisory Committee (GMAC), the Therapeutic Goods Administration (TGA) and subsequently by the Gene Technology Regulator under DIR 033. The licence for DIR 033 was issued to CSL Ltd on 20 June 2003 and was surrendered at the licence holder's request on 14 September 2010.</p> <ul style="list-style-type: none"> Orochol® was previously registered for commercial sale in several other countries including Switzerland, Austria, Finland, Canada, New Zealand, Sri Lanka, the Philippines and several South American countries. <p><u>Vaxchora®:</u></p> <ul style="list-style-type: none"> Clinical trials with PXVX0200 (trade name Vaxchora®) were approved and conducted in the United States (US) to study the safety and effectiveness of the vaccine in preventing cholera. Clinical trials (limited and controlled release) of this GMO as a human vaccine (PXVX0200, trade name Vaxchora®) were approved by the Gene Technology Regulator under DIR 126. This was to confirm the safety and efficacy of the newly manufactured product. The licence for DIR 126 was issued to PaxVax Australia Pty Ltd on 10 April 2014 and was surrendered at the licence holder's request on 10 September 2020.
Current approvals	<ul style="list-style-type: none"> Vaxchora® has been approved for oral administration by the Food and Drug Administration (FDA) for adults and by the European Medicines Agency (EMA) for adults and children aged 6 years and older traveling to cholera-affected areas.
Proposed locations	Australia-wide for travellers
Primary purpose	Commercial supply of the GM cholera vaccine

Risk assessment

The risk assessment concludes that risks to the health and safety of people or the environment from the proposed dealings, either in the short or long term, are negligible. No specific risk treatment measures are required to manage these negligible risks.

The risk assessment process considered how the genetic modification and activities conducted with the GMO 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, relevant previous approvals, current scientific knowledge and advice received from a wide range of experts, agencies and authorities consulted on the preparation of the RARMP. Both the short and long term risks were considered.

Credible pathways to potential harm that were considered included: whether people and animals can be inadvertently exposed to the GMO, the potential for the reversion of GMO to the toxigenic phenotype and the potential for transfer of genetic material to and from the GMO. The potential for GMO to be released into the environment and its effects was also considered.

The principal reasons for the conclusion of negligible risks were that: the genetic modifications make the GMO unable to cause disease therefore are unlikely to cause harm to people or the environment; genes similar to the introduced genes are naturally present in the environment; *V. cholerae* does not cause disease in other organisms; likelihood of reversion of GMO to a toxigenic strain is very low and the impact of persistence of the small numbers of GMO in the Australian aquatic environment is negligible.

Risk management

The risk management plan concluded that risks from the proposed dealings can be managed so as to protect people and the environment by imposing general conditions to ensure that there is ongoing oversight of the release.

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 evaluated identified risks and considered general risk management measures. The risk management plan is given effect through licence conditions.

As the level of risk was assessed as negligible, specific risk treatment is not required. However, the Regulator has drafted licence conditions regarding post-release review (PRR) to ensure that there is ongoing oversight of the supply of the GM cholera vaccine and to allow the collection of information to verify the findings of the RARMP. The draft licence, detailed in Chapter 4 of the consultation RARMP, also contains a number of general conditions relating to ongoing licence holder suitability, auditing and monitoring, and reporting requirements, which include an obligation to report any unintended effects.