Australian Government
Department of Health
Office of the Gene Technology Regulator

30 September 2021

Summary of the Risk Assessment and Risk Management Plan

(Consultation Version) for

Licence Application DIR 185

Introduction

The Gene Technology Regulator (the Regulator) has received a licence application to conduct a clinical trial using a live attenuated genetically modified (GM) *Bordetella pertussis* (BPZE1) as a vaccine for whooping cough. It qualifies as Dealings involving the Intentional Release (DIR) of genetically modified organisms into the Australian environment under the *Gene Technology Act 2000*.

The applicant, Novotech (Australia) Pty Ltd (Novotech) proposes to conduct a clinical trial with BPZE1 to evaluate the immunological response and safety of BPZE1 as a whooping cough vaccine in school age children. This clinical trial involves the intranasal administration of the GM vaccine.

B. pertussis causes a respiratory disease that results in persistent coughing commonly known as 'whooping cough'. It is highly infectious in unvaccinated people. In Australia, pertussis epidemics usually occur every 3-4 years despite a longstanding pertussis immunisation program. The vaccine will be manufactured overseas and imported directly to the clinical trial site in Australia. The applicant proposes to administer the GM vaccine to a limited number of healthy participants.

Clinical trials in Australia are conducted in accordance with requirements of the *Therapeutic Goods Act 1989*, which is administered by the Therapeutic Goods Administration (TGA). Therefore, in addition to approval by the Regulator, Novotech will require authorisation from TGA before the trial commences. Clinical trials conducted in Australia must also be conducted in accordance with the National Statement on Ethical Conduct in Human Research and with the Guidelines for Good Clinical Practice of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Novotech will also require approval from the Department of Agriculture, Water and the Environment for import of the GMO.

The Regulator has prepared a Risk Assessment and Risk Management Plan (RARMP) for this application, which concludes that the proposed supply of the GM vaccine poses negligible risks to human health and safety and the environment. Licence conditions have been drafted for the proposed supply. The Regulator invites submissions on the RARMP, including draft licence conditions, to inform the decision on whether to issue a licence.

The application

Application number	DIR-185
Applicant	Novotech (Australia) Pty Ltd

Project title	Clinical trial with a live attenuated genetically modified *Bordetella pertussis* as a vaccine for the treatment of whooping cough[1]
Parent organism	*Bordetella pertussis* (Tohama I strain)
Introduced gene and modified trait	*B. pertussis* toxins have been modified or deleted as below: • Modification of pertussis toxin; *PTX* gene – removal of toxicity • Replacement of *ampG* gene - 100-fold reduction of tracheal cytotoxin (TCT) production • Deletion of dermonecrotic toxin; *DNT* gene - no production of DNT
Principle purpose	The proposed trial is a Phase 2b study designed to assess the immunological response and safety profile of the single dose of BPZE1 with and without the standard tetanus, diphtheria and pertussis vaccine in healthy school age children.
Previous clinical trials	Several clinical trials have been completed in healthy adults. Details of the trials are summarised below: Phase 1: Safety and immunogenicity; January 2012 (NCT0118512) Phase 1b: Testing higher dose; December 2017 (NCT02453048) Phase 2a: Dose response; May 2020 (NCT03541499) Phase 2b: Multiple doses; June 2020 (NCT03942406)
Proposed locations	This clinical trial would be conducted within clinical trial sites in Australia. The number of sites and specific locations are yet to be determined.
Proposed limits and controls	• The GMO would be administered to trial participants within a suitable medical facility. • Number of participants would be restricted (~300 participants). • Storage areas within clinical facilities would be limited to authorised personnel. • Staff handling the GMO would be trained and wear personal protective equipment. • Waste that may contain the GMO would be disposed of as infectious material (i.e. via the clinical waste stream). • Participants would remain at the clinical trial site for a specified duration after administration and provided with detailed instructions on hygiene measures e.g., sneezing/coughing etiquette and hand washing instruction. • Participants with frequent contact with children younger than 6 months of age; participants who live in the same household with individuals with known immunodeficiency; or individuals on immunosuppressant therapy would be excluded from the trial. • Import, transport and storage of the GMO would be carried out in accordance with the OGTR's *Guidelines for the Transport, Storage and Disposal of GMOs*.

[1] The title of the licence application submitted by Novotech (Australia) Pty Ltd is "Clinical trials with BPZE1".

Risk assessment

The risk assessment concludes that risks to the health and safety of people or the environment from the proposed clinical trial are negligible. No specific risk treatment measures are required to manage these negligible risks.

The risk assessment process considers how the genetic modifications and proposed activities conducted with the GMO might lead to harm to people or the environment. Risks are characterised in relation to both the seriousness and likelihood of harm, considering information in the application (including proposed controls), relevant previous approvals and current scientific/technical knowledge. Both the short- and long-term impact are considered.

Credible pathways to potential harm that were considered include the; potential exposure of people and animals to the GMO; and the potential for the GMO to transfer or acquire genetic material from other bacteria. The potential for the GMO to be released into the environment and its effects were also considered.

Important factors in reaching the conclusions of the risk assessment included:

- The GMO is attenuated and unable to produce toxins responsible for disease;
- The likelihood of accidental exposure to the GMO in people not being vaccinated (non-vaccinees) would be minimised due to proper work practices and well-established import, transport, storage and disposal procedures;
- The likelihood of recombination of the GMO with other bacteria resulting in the restoration of its toxigenic function is very low; and
- The availability of antibiotic treatment for the GMO.

As risks to the health and safety of people, or the environment, from the proposed trial of the GM vaccine have been assessed as negligible, the Regulator considers that the dealings involved do not pose a significant risk to either people or the environment.

Risk management

The risk management plan describes measures to protect the health and safety of people and to protect the environment by controlling or mitigating risk. The risk management plan is given effect through licence conditions. Draft licence conditions are detailed in Chapter 4 of the RARMP.

As the level of risk is considered negligible, specific risk treatment is not required. However, since this is a clinical trial, the draft licence includes limits on the number of trial participants, locations limited to hospitals and clinical trial sites, limits on the duration of the trial, as well as a range of controls to minimise the potential for the GMO to spread in the environment. In addition, there are several general conditions relating to ongoing licence holder suitability, auditing and monitoring, and reporting requirements which include an obligation to report any unintended effects.